

SUPPLEMENTAL MATERIAL

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51 **Supplemental 1. PROSPERO registration.**
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PROSPERO
International prospective register of systematic reviews

NHS
National Institute for
Health Research



Animal review

1. * Review title.

Give the working title of the review. This must be in English. The title should have the interventions or exposures being reviewed and the associated health or social problems.

Safety and efficacy of cell-based/derived therapies in congenital heart disease; a systematic review and meta analysis of pre-clinical and clinical studies

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

English

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

27/08/2019

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

01/01/2020

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.

Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.

This field should be updated when any amendments are made to a published record and on completion and publication of the review.

The review has not yet started: No

| Review stage | Started | Completed |
|---|---------|-----------|
| Preliminary searches | No | Yes |
| Piloting of the study selection process | No | Yes |
| Formal screening of search results against eligibility criteria | No | Yes |
| Data extraction | No | Yes |
| Risk of bias (quality) assessment | Yes | No |
| Data analysis | Yes | No |
| Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised). | | |

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Alvaro Moreira

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Moreira

7. * Named contact email.

Enter the electronic mail address of the named contact.
MoreiraA@uthscsa.edu

8. * Named contact address.

Enter the full postal address for the named contact.
UT Health San Antonio Department of Pediatrics, Division of Neonatology 7703 Floyd Curl Drive MC 7812 San Antonio, TX, USA 78229

9. Named contact phone number

Enter the telephone number for the named contact, including international dialling code.
210-567-5226

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'none' if the review is not affiliated to any organisation.
UT Health San Antonio

Organisation web address:

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country are**

now mandatory fields for each person.

Dr John Martinez. UT Health Pediatrics

Dr Sarah Zoretic. UT Health Pediatrics

Dr Alvaro Moreira. UT Health San Antonio, Department of Pediatrics, Division of Neonatology

12. * Funding sources/sponsors.

Give details of the individuals, organisations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.

Parker B. Francis

Grant number(s)

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

15. * Review question.

Give details of the question to be addressed by the review, clearly and precisely.

Are cell-based/derived therapies both safe and efficacious in clinical trials involving congenital heart disease?

Context and rationale

Provide a brief description of the context and rationale of the review, including information on the relevance of your review for human health (max 250 words).

Preclinical studies have established that regenerative therapies show promise as primary/adjunctive therapies for congenital heart disease (CHD). Animal models have demonstrated that regenerative cells are safe and effective. As these therapies have now translated to clinical trials in pediatric CHD, it is imperative to summarize the current findings and identify knowledge gaps that still remain in order optimize translational success. Therefore, the purpose of this systematic review and meta-analysis is twofold: (i) assess the safety, and (ii) efficacy of cell-based/derived therapies in animal models of congenital heart disease.

16. * Searches.

Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

MEDLINE via PubMed, Scopus, ScienceDirect, Web of Science, Reference lists of included studies,

Reference lists of relevant reviews Search dates: no restriction on timeline of search results (initial

year-08/26/19)Restrictions on language: no restrictions Publication: no publication date restrictions Will

searches be re-run prior to final analysis? : yes Will unpublished studies be sought? : no

17. URL to search strategy.

Give a link to the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies).

MEDLINE PubMed: (((((((((((((((((((regenerative[MeSH Terms]) OR regenerative) OR stem cell) OR stromal cell) OR mesenchymal) OR embryonic) OR pluripotent) OR multipotent) OR inducible pluripotent) OR progenitor) OR hematopoietic) OR umbilical cord) OR cord blood) OR c-kit) OR secretome) OR microRNA) OR exosome) OR microvesicle) OR microparticle) OR extracellular vessicle))) AND (((((((((((((((truncus arteriosus) OR transposition of great arteries) OR transposition of great vessels) OR tricuspid atresia) OR hypoplastic right heart syndrome) OR hypoplastic left heart syndrome) OR single ventricle) OR tetralogy of fallot) OR total anomalous pulmonary venous return) OR pulmonary atresia) OR coarctation of aorta) OR interrupted aortic arch) OR doublet outlet right ventricle) OR single inlet ventricle)

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Human disease modelled.

Give a short description of the disease, condition or healthcare domain being modelled.

Congenital heart disease

19. * Animals/population.

Give summary criteria for the animals being studied by the review, e.g. species, sex, details of disease model. Please include details of both inclusion and exclusion criteria.

Inclusion criteria:

Human: Children (newborn-18 years) with congenital heart disease to include adults with history of congenital heart disease receiving cell-based/derived therapies
Animal models of congenital heart disease

Exclusion criteria:

Human: Children without congenital heart disease, Adults without congenital heart disease receiving cell-based/derived therapies, Adult models of heart disease

Animal: Animal models without congenital heart disease

20. * Intervention(s), exposure(s).

Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed (e.g. dosage, timing, frequency). Please include details of both inclusion and exclusion criteria.

Inclusion criteria:

The following will be used for both human and animal studies. Regenerative cell-based/derived therapy used to treat congenital heart disease. Regenerative cell therapies will be defined as: mesenchymal, embryonic, multipotent, inducible pluripotent cells, progenitor, hematopoietic, umbilical cord, cord blood, c-kit+, secretome, exosome, microRNA, microvesicles, extracellular vesicles.

Exclusion criteria:

The following will be used for both human and animal studies. Non cell-based/derived therapies used to treat congenital heart disease

21. * Comparator(s)/control.

Where relevant, give details of the type(s) of control interventions against which the experimental condition(s) will be compared (e.g. another intervention or a non-exposed control group). Please include details of both inclusion and exclusion criteria.

Inclusion criteria:

Human: Placebo. Children with congenital heart disease who did not receive cell based therapies.

Animal: Animals in experimental models not subject to cell-based/derived therapies for the treatment of congenital heart disease (placebo and sham).

Exclusion criteria:

Human: Children without congenital heart diseases

Animal: Animals not modeling congenital heart disease

22. * Study designs to be included.

Give details of the study designs eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. Please include details of both inclusion and exclusion criteria.

Inclusion criteria:

Clinical trials, cohort, case reports

Exclusion criteria:

Articles not assessing outcomes of interest

23. Other selection criteria or limitations applied.

Give details of any other inclusion and exclusion criteria, e.g. publication types (reviews, conference abstracts), publication date, or language restrictions.

Review articles, book chapters, abstracts will be excluded. No restrictions placed based on publication date or language.

24. * Outcome measure(s).

Give detail of the outcome measures to be considered for inclusion in the review. Please include details of both inclusion and exclusion criteria.

Inclusion criteria:

The following outcome measures will be used for both human and animal studies

Cardiac function, as measured by:

-Right/Left ejection fraction-End diastolic volume-End systolic volume-Tricuspid annular plane systolic excursion-Fractional area change-Fractional shortening Safety: -Mortality -Adverse events with administration (fever, rash, infection, hemodynamic instability, arrhythmia, etc)

Exclusion criteria:

Animal or human studies not assessing safety or efficacy (as defined above) after cell-based/derived.

25. N/A.

This question does not apply to systematic reviews of animal studies for human health submissions.

26. * Study selection and data extraction.

Procedure for study selection

Give the procedure for selecting studies for the review, including the screening phases (title and/or title-abstract and/or full-text), the number of researchers involved, and how discrepancies will be resolved.

Study selection: a) Two investigators (J. Martinez & S. Zoretic) will independently screen all the abstracts/full texts for the inclusion criteria. b) Differences of opinion in either phase that cannot be resolved by discussion will be resolved by consulting a third investigator (A. Moreira).

Prioritise the exclusion criteria

Multiple exclusion criteria may apply to an abstract/paper, which can cause discrepancies between reviewers in the reason for exclusion recorded. To avoid this, it is helpful to prioritize the exclusion criteria (e.g. 1) not an animal study; 2) not a myocardial infarction model, etc.) and record the highest ranking applicable criterion as the reason for exclusion. Please sort the exclusion criteria defined in questions 19 to 24. If applicable, do so for each screening phase.

1) in-vitro studies 2) studies not including cell-based/derived therapies 3) Human studies not including congenital heart disease models 4) Animal models without congenital heart disease 5) Animal or human studies not assessing safety or efficacy (as defined above) after cell-based/derived. 6) Adults without congenital heart disease receiving cell-based/derived therapies 7) Adult models of heart disease 8) Review articles, book chapters, abstracts

Methods for data extraction

Describe methods for data extraction, including the number of reviewers performing data extraction, extraction of data from text and/or graphs, whether and how authors of eligible studies will be contacted to provide missing or additional data, etc.

Data extraction: Study design, methodology, patient demographics, clinical diagnoses, cell characteristics (source, dose, frequency and delivery), cardiac imaging parameters, laboratory values, publication details (author, year, funding, etc), follow up data a) Two investigators (J. Martinez & S. Zoretic) will independently screen all the abstracts/full texts for the inclusion criteria. b) Differences of opinion in either phase that cannot be resolved by discussion will be resolved by consulting a third investigator (A. Moreira). Data will be extracted from text, tables and figures (webplot digitizer). For missing data, will contact authors. Data will be recorded via excel spreadsheet.

Data to be extracted: study design

Specify the data to be extracted related to characteristics of the study design, e.g. controlled versus cross-over, number of experimental groups, etc.

Humans: Number of children in experimental +/- control group, number of experimental groups, phase of clinical trial, cell-based/derived therapies parameters (dose, frequency, route, etc), cardiac assessments (echo, MRI, CT, biomarkers), time points for data collection

Animals: Number of animals in experimental +/- control group, number of experimental groups, cell-based/derived therapies parameters (dose, frequency, route, etc), cardiac assessments (echo, MRI, CT, biomarkers), time points for data collection

Data to be extracted: animal model

Specify the data to be extracted related to characteristics of the animal model, e.g. species, sex of the animals, etc.

Number of animals in experimental and control groups, power calculation reported, method(s) to induce congenital heart disease, animal species/strain, age, gender, weight and immune status.

Data to be extracted: intervention of interest

Specify the data to be extracted related to characteristics of the intervention of interest, e.g. dose, timing, etc.

Cell type, tissue source, dose, mode of delivery, frequency, timing, passage number

Data to be extracted: primary outcome(s)

Define the primary outcome measure(s). For each outcome measure, specify in which format data will be extracted, including the eligible units of measurement, and data type (continuous/dichotomous). A description of any other manipulation or transformation of the extracted data that is planned may be included.

The following outcomes will be assessed in both animal and human studies

Safety:

-Mortality (dichotomous) -Adverse events with administration (fever, rash, infection, hemodynamic instability, arrhythmia, etc) (dichotomous)

Assessment of cardiac function as measured by:

-Right/Left ejection fraction (% , continuous)-End diastolic volume (mL, continuous)-End systolic volume (mL, continuous) -Tricuspid annular plane systolic excursion (mm, cm, continuous) -Fractional area change (% , continuous) -Fractional shortening (% , continuous)

Data to be extracted: secondary outcome(s)

Define the secondary outcome measure(s). For each outcome measure, specify in which format data will be extracted, including the eligible units of measurement, and data type (continuous/dichotomous). A description of any other manipulation or transformation of the extracted data that is planned may be included.

n/a

Data to be extracted: other

Specify any other data or study characteristics to be extracted, e.g. bibliographical details, such as author, year and language.

Author, year, funding, title, language, contact author email, journal

27. * Risk of bias and/or quality assessment.

State whether and how risk of bias and/or study quality will be assessed. Assessment tools specific for pre-clinical animal studies include SYRCLE's risk of bias tool and the CAMARADES checklist for study quality

No risk of bias and/or quality assessment planned

No

By use of SYRCLE's risk of bias tool

Yes

By use of SYRCLE's risk of bias tool adapted as follows:

No

By use of the CAMARADES checklist for study quality

No

By use of the CAMARADES checklist for study quality, adapted as follows:

No

Other criteria, namely

Yes

Animal: SYRCLE Risk of bias

Human non randomized: Robins-I

Human randomized: Cochrane Risk of bias

Method for risk of bias and/or quality assessment

Give the procedure for the risk of bias and/or quality assessment, including the number of reviewers involved, their contribution, and how discrepancies will be resolved.

Two separate reviewers will assess risk of bias for each study. Discrepancies will be resolved by senior author.

28. * Strategy for data synthesis.

Planned approach

For each outcome measure, specify whether a quantitative or narrative synthesis is planned and how this decision will be made.

Quantitative synthesis will be preferred method for reporting information, however if 4 studies are assessing a particular outcome we will conduct a narrative explanation as, too few studies will be available to conduct meta-analysis.

If a meta-analysis is planned, please specify the following:

Effect measure

For each outcome measure, specify the effect measure to be used (e.g. mean difference, odds ratio etc.).

Animal studies: standardized mean difference

Human studies: odds ratio

Effect models

For each outcome measure, specify the statistical model of analysis (e.g. random-effects or fixed-effect model).

Random-effects model

Heterogeneity

Specify the statistical methods to assess heterogeneity (e.g. I^2 , Q). For further guidance please refer to the [introduction](#) and [practical guide](#) to pre-clinical meta-analysis.

I^2

Other

Specify other details of the meta-analysis methodology (e.g. correction for multiple testing, correction for multiple use of control group).

n/a

29. * Analysis of subgroups or subsets.

Subgroup analyses

Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response

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if no subgroup analyses are planned.

Study design: experimental and control groups, congenital heart disease model, measures of safety

measures of function, outcome time

Animal models: species, strain, age, gender

Cell-based/derived therapy source: dose, delivery, timing, frequency, transplant method (allogeneic, xenogeneic, autologous)

Sensitivity

For each outcome measure, specify any sensitivity analyses you propose to perform.

If high heterogeneity is observed (70%), subgroup analyses will be conducted

Publication bias

Specify whether an assessment of publication bias is planned. If applicable, specify the method for assessment of publication bias.

funnel plot assessment, Egger's regression

30. * Review type.

Type of review

Animal model review

No

Experimental animal exposure review

No

Pre-clinical animal intervention review

Yes

31. Language.

Select each country individually to add it to the list below, use the bin icon to remove any added in error.

English

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

United States of America

33. Other registration details.

List other places where the systematic review protocol is registered. The name of the organisation and any unique identification number assigned to the review by that organisation should be included.

n/a

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one.

n/a

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

The manuscript will be submitted to a leading journal in field. In addition, a report will be submitted to the funder (Parker B Francis foundation).

Do you intend to publish the review on completion?

No

36. * Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line.

Regenerative medicine, cell-based/derived therapies, stem cells, congenital heart disease, human, clinical trials, animal studies

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

Previous manuscript focusing on cell-based/derived therapies as a treatment for right ventricular dysfunction is currently being considered for publication.

38. * Current review status.

Review status should be updated when the review is completed and when it is published.

Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

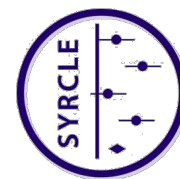
Provide any further information the review team consider relevant to the registration of the review.

40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available. Give the full citation for the final report or publication of the systematic review.

Give the link to the published review.

Supplemental 2. SYRCLE criteria for animal intervention studies.



SYSTEMATIC REVIEW PROTOCOL FOR ANIMAL INTERVENTION STUDIES

FORMAT BY SYRCLE (WWW.SYRCLE.NL)

VERSION 2.0 (DECEMBER 2014)

| Item # | Section/Subsection/Item | Description | Check for approval |
|----------------------|---|---|--------------------|
| A. General | | | |
| 1. | Title of the review | Safety and efficacy of cell-based therapies in congenital heart disease; a systematic review and meta analysis of pre-clinical and clinical studies | |
| 2. | Authors (names, affiliations, contributions) | John Martinez, MD: conception, study design, search, data collection, protocol writing, manuscript writing Sarah Zoretic, DO: conception, study design, search, data collection, protocol writing, manuscript writing Alvaro Moreira MD, MSc: conception, study design, data collection and analysis, manuscript revision, supervision University of Texas Health San Antonio Department of Pediatrics, Division of Neonatology, | |
| 3. | Other contributors (names, affiliations, contributions) | None | |
| 4. | Contact person + e-mail address | Alvaro Moreira: MoreiraA@uthscsa.edu | |
| 5. | Funding sources/sponsors | Parker B Francis Foundation | |
| 6. | Conflicts of interest | None | |
| 7. | Date and location of protocol registration | CAMARADES | |
| 8. | Registration number (if applicable) | N/A | |
| 9. | Stage of review at time of registration | Preliminary searches | |
| B. Objectives | | | |
| Background | | | |
| 10. | What is already known about this disease/model/intervention? Why is it important to do this review? | Preclinical studies have established that regenerative therapies show promise as primary/adjunctive therapies for congenital heart disease (CHD). Animal models have demonstrated that regenerative cells are safe and effective. As these therapies have now translated to clinical trials in pediatric CHD, it is imperative to summarize the current findings and identify knowledge | |

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| | | gaps that still remain in order optimize translational success. Therefore, the purpose of this systematic review and meta-analysis is twofold: (i) assess the safety, and (ii) efficacy of cell-based/derived therapies in animal models of congenital heart disease. | |
| Research question | | | |
| 11. | Specify the disease/health problem of interest | Congenital heart disease: Hypoplastic left heart syndrome, Tricuspid atresia, Single ventricle physiology, Transposition of great arteries, Tetralogy of Fallot, Pulmonary Atresia, Anomalous pulmonary venous return, Double outlet right ventricle, Single inlet ventricle, Coarctation of aorta, Interrupted aortic arch, Ebstein's anomaly. | |
| 12. | Specify the population/species studied | Animal models of congenital heart disease (as listed above) | |
| 13. | Specify the intervention/exposure | Cell-based/derived therapies: mesenchymal, embryonic, multipotent, inducible pluripotent cells, progenitor, hematopoietic, umbilical cord, cord blood, c-kit+, secretome, exosome, microRNA, microvesicle, extracellular vesicle. | |
| 14. | Specify the control population | Placebo or no treatment | |
| 15. | Specify the outcome measures | Primary Outcome: Safety and cardiac function (refer to number 26) | |
| 16. | State your research question (based on items 11-15) | Are cell-based/derived therapies both safe and efficacious in experimental models of congenital heart disease? | |
| C. Methods | | | |
| Search and study identification | | | |
| 17. | Identify literature databases to search (e.g. Pubmed, Embase, Web of science) | <input checked="" type="checkbox"/> MEDLINE via PubMed <input checked="" type="checkbox"/> Web of Science <input checked="" type="checkbox"/> SCOPUS <input type="checkbox"/> EMBASE <input checked="" type="checkbox"/> Other, namely: Science direct <input type="checkbox"/> Specific journal(s), namely: | |
| 18. | Define electronic search strategies (e.g. use the step by step search guide ¹⁵ and animal search filters ^{20, 21}) | When available, please add a supplementary file containing your search strategy: [insert file name] | |
| 19. | Identify other sources for study identification | <input checked="" type="checkbox"/> Reference lists of included studies <input type="checkbox"/> Books <input checked="" type="checkbox"/> Reference lists of relevant reviews <input type="checkbox"/> Conference proceedings, namely: <input type="checkbox"/> Contacting authors/ organisations, namely: <input type="checkbox"/> Other, namely: | |
| 20. | Define search strategy for these other sources | Screening the reference lists for relevant titles and screening the abstracts of these relevant titles | |
| Study selection | | | |

| | | | |
|--|--|---|--|
| 21. | Define screening phases (e.g. pre-screening based on title/abstract, full text screening, both) | First phase: screening by title and abstract Second phase: full text screening of eligible articles Full text studies that do not meet inclusion will be incorporated into the flow diagram with reasons for exclusion | |
| 22. | Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved | a) Two investigators (J. Martinez & S. Zoretic) will independently screen all the abstracts/full texts for the inclusion criteria. b) Differences of opinion in either phase that cannot be resolved by discussion will be resolved by consulting a third investigator (A. Moreira). | |
| <i>Define all inclusion and exclusion criteria based on:</i> | | | |
| 23. | Type of study (design) | Inclusion criteria: pre-clinical studies Exclusion criteria: non-intervention studies, no control group, co-intervention studies | |
| 24. | Type of animals/population (e.g. age, gender, disease model) | Inclusion criteria: animal models of congenital heart disease, all genders Exclusion criteria: humans, in-vitro, non-pediatric models of heart disease | |
| 25. | Type of intervention (e.g. dosage, timing, frequency) | Inclusion criteria: administration of cell-based/derived therapy- all dosages, timing, and frequency; cells may be derived from any tissue source Exclusion criteria: Cardiac administration of cell-based/derived therapy assessing for variables other than safety or effect on function. | |
| 26. | Outcome measures | <u>Cardiac function as measured by:</u> -Right/Left ejection fraction -End diastolic volume -End systolic volume -Tricuspid annular plane systolic excursion -Fractional area change -Fractional shortening <u>Safety:</u> -Mortality -Adverse events with administration (fever, rash, infection, hemodynamic instability, arrhythmias, etc) Exclusion criteria: | |
| 27. | Language restrictions | Inclusion criteria: English and Spanish Exclusion criteria: All other languages | |
| 28. | Publication date restrictions | Inclusion criteria: no publication date restrictions Exclusion criteria: | |
| 29. | Other | Inclusion criteria: Exclusion criteria: | |
| 30. | Sort and prioritize your exclusion criteria per selection phase | <u>Selection phase:</u> title and abstract screening 1. Not a primary study 2. Not an in vivo animal study | |

| | | | |
|--|---|--|--|
| | | 3. Not congenital heart disease 4. No cell based/derived therapy use 5. Adult animal <u>Selection phase: full text screening</u> 1. Not a primary study 2. Not an in vivo animal study 3. Not congenital heart disease 4. No cell based/derived therapy use 5. No assessment of safety, effect on ventricular function 5. No control group 6. Co-intervention studies | |
| Study characteristics to be extracted (for assessment of external validity, reporting quality) | | | |
| 31. | Study ID (e.g. authors, year) | Authors, journal, title, year, language, contact author e-mail | |
| 32. | Study design characteristics (e.g. experimental groups, number of animals) | Number of animals in experimental and control groups, reporting of randomization process, power calculation reported, method(s) to induce congenital heart disease | |
| 33. | Animal model characteristics (e.g. species, gender, disease induction) | Animal species, strain, age, gender, weight, and immune status | |
| 34. | Intervention characteristics (e.g. intervention, timing, duration) | Source, dose, delivery, timing, and frequency of intervention | |
| 35. | Outcome measures | Assessment of safety as defined through mortality or occurrence of adverse events upon administration. | |
| 36. | Other (e.g. drop-outs) | Assessment of cardiac function through measures as noted above | |
| Assessment risk of bias (internal validity) or study quality | | | |
| 37. | Specify (a) the number of reviewers assessing the risk of bias/study quality in each study and (b) how discrepancies will be resolved | a) Two investigators (J. Martinez & S. Zoretic) will independently screen all the abstracts/full texts for the inclusion criteria. b) Differences of opinion in either phase that cannot be resolved by discussion will be resolved by consulting a third investigator (A. Moreira) | |
| 38. | Define criteria to assess (a) the internal validity of included studies (e.g. selection, performance, detection and attrition bias) and/or (b) other study quality measures (e.g. reporting quality, power) | X By use of SYRCLE's Risk of Bias tool⁴ <input type="checkbox"/> By use of SYRCLE's Risk of Bias tool, adapted as follows: <input type="checkbox"/> By use of CAMARADES' study quality checklist, e.g.²² <input type="checkbox"/> By use of CAMARADES' study quality checklist, adapted as follows: <input type="checkbox"/> Other criteria, namely: | |
| Collection of outcome data | | | |
| 39. | For each outcome measure, define the type of data to be extracted (e.g. continuous/dichotomous, unit of measurement) | All outcome measures will be expressed through study units of measure, values expressed as continuous measures will be recorded as means +/- SD, SEM or median +/- IQR | |

| | | | |
|--|---|--|-------|
| 40. | Methods for data extraction/retrieval (e.g. first extraction from graphs using a digital screen ruler, then contacting authors) | Extraction from text, tables, and figures (GetData graph digitizer 2.26) Contact authors in case of missing data | |
| 41. | Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved | a) Two investigators (J. Martinez & S. Zoretic) will independently screen all the abstracts/full texts for the inclusion criteria. b) Differences of opinion in either phase that cannot be resolved by discussion will be resolved by consulting a third investigator (A. Moreira) | |
| Data analysis/synthesis | | | |
| 42. | Specify (per outcome measure) how you are planning to combine/compare the data (e.g. descriptive summary, meta-analysis) | For sufficient data, we will conduct a meta-analysis for eligible studies. If insufficient data to measure outcomes, we will provide a descriptive summary of study results | |
| 43. | Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed | A minimum of 4 articles for the same outcome is required. High heterogeneity is expected between studies due to differences in the study designs. We will perform a meta-regression analysis to investigate sources of heterogeneity. | |
| <i>If a meta-analysis seems feasible/sensible, specify (for each outcome measure):</i> | | | |
| 44. | The effect measure to be used (e.g. mean difference, standardized mean difference, risk ratio, odds ratio) | Continuous outcomes will be analysed using standardized mean differences (95% CI) | |
| 45. | The statistical model of analysis (e.g. random or fixed effects model) | Random effects model | |
| 46. | The statistical methods to assess heterogeneity (e.g. I^2 , Q) | I^2 | |
| 47. | Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis) | Study design: experimental and control groups, congenital heart disease model, measures of safety, measures of cardiac function. Animal model: species, strain, age, gender Cell based/derived therapy source: dose, delivery, timing, frequency, transplant method (allogeneic, xenogeneic, autologous, etc.) | |
| 48. | Any sensitivity analyses you propose to perform | If high heterogeneity is observed ($\geq 70\%$), subgroup analyses will be conducted | |
| 49. | Other details meta-analysis (e.g. correction for multiple testing, correction for multiple use of control group) | N/A | |
| 50. | The method for assessment of publication bias | Funnel plot assessment Egger's regression | |
| | | | |
| Final approval by (names, affiliations): | | John Martinez MD Sarah Zoretic DO Alvaro Moreira MD, MSc | Date: |

Supplemental 3. Database search terms.

Database Search Terms:

("regenerative" OR "stem cell" OR "stromal cell" OR "mesenchymal" OR "embryonic" OR "pluripotent" OR "multipotent" OR "inducible pluripotent" OR "progenitor" OR "hematopoietic" OR "umbilical cord" OR "cord blood" OR "microparticle" OR "extracellular vesicles") AND ("tetralogy of fallot" or "single ventricle" or "transposition of great arteries" or "anomalous pulmonary venous" or "tricuspid atresia" or "truncus arteriosus" or "hypoplastic left heart" or "ebstein" or "double outlet right ventricle" or "hypoplastic right heart" or "pulmonary atresia" or "coarctation of aorta" or "interrupted aortic arch" or "single inlet ventricle")

Supplemental 4. List of included studies.

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 183 *Cardiol Young* 2012;**22**:558–563.
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PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|------------------------------------|----|---|--------------------|
| TITLE | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 2 |
| ABSTRACT | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 3 |
| INTRODUCTION | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4 |
| METHODS | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 5 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 5-6 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 5 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 5 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 5 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 5-6 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 5-6 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 8 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 7-8 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis. | 7-8 |

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PRISMA 2009 Checklist

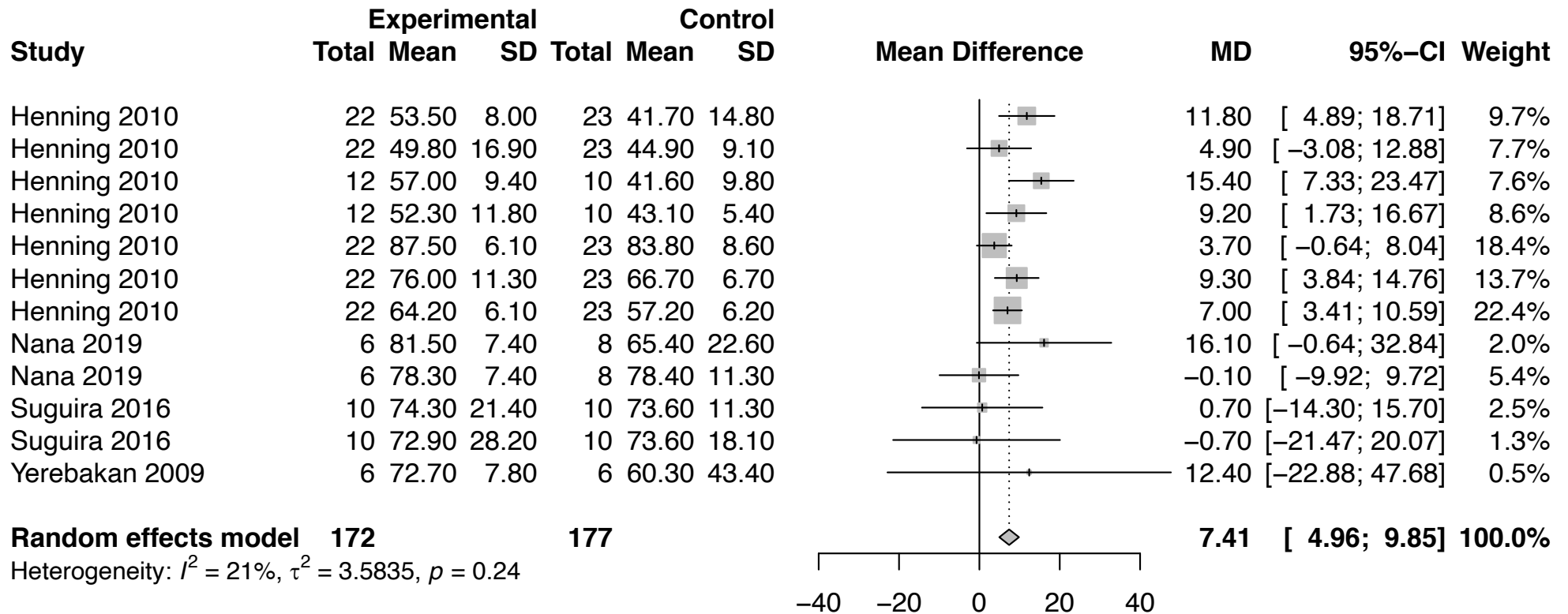
| Section/topic | # | Checklist item | Reported on page # |
|-------------------------------|----|--|--------------------|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 8 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 7-8 |
| RESULTS | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 9 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 9, 11 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 13-14 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 9-13 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 9-13 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 13-14 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 10-11, 12-13 |
| DISCUSSION | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 15-18 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 18 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 19 |
| FUNDING | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 19 |

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

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261 **Supplemental 6. Effect size of regenerative cell on animal ejection fraction.** Forest plots demonstrating MD
 262 and 95% CI for A) Left ventricular ejection fraction; cell-based n=172; control=177; p <0.0001. B) Right
 263 ventricular ejection fraction; cell-based n=84; control n=84; p=0.02. C) Disease model; cell-based n= 256; control
 264 n=261; RVHF, p=0.01; DCM, p<0.0001.
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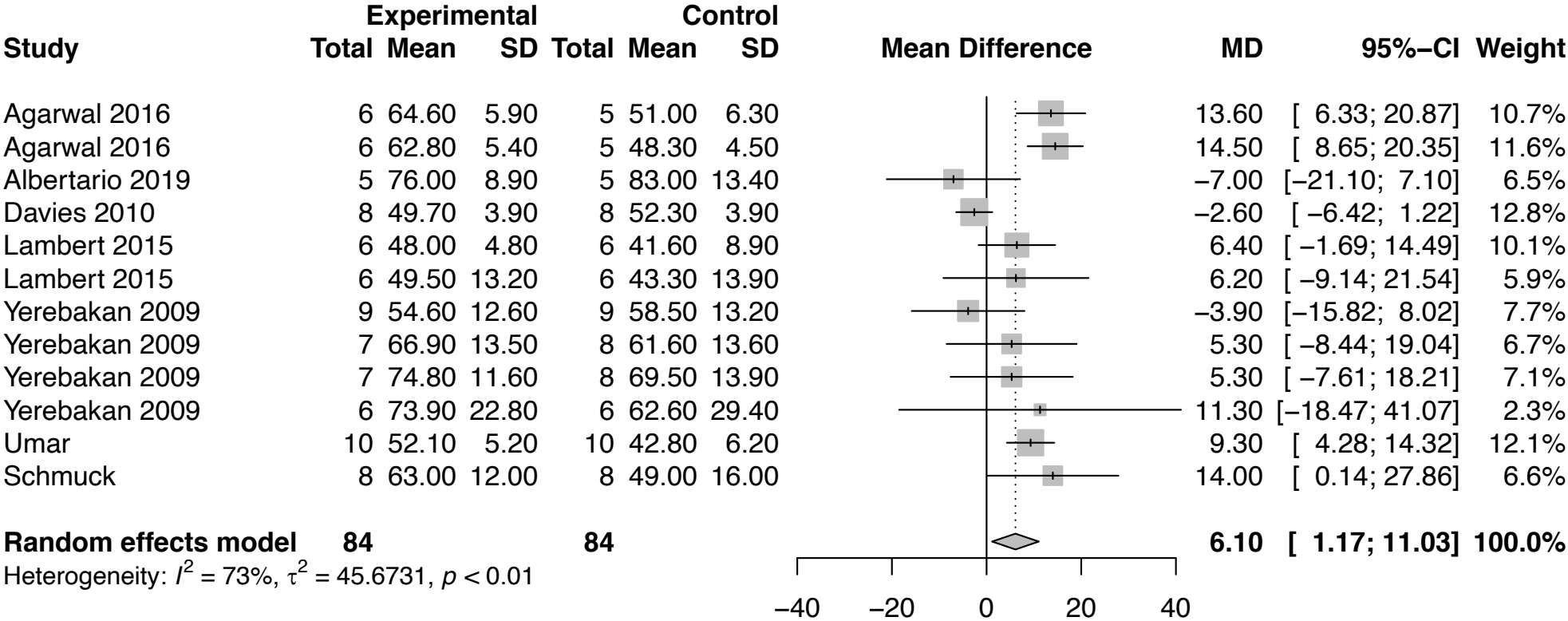
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267 **Supplemental 6. A) Cell-based effect on animal LVEF.**

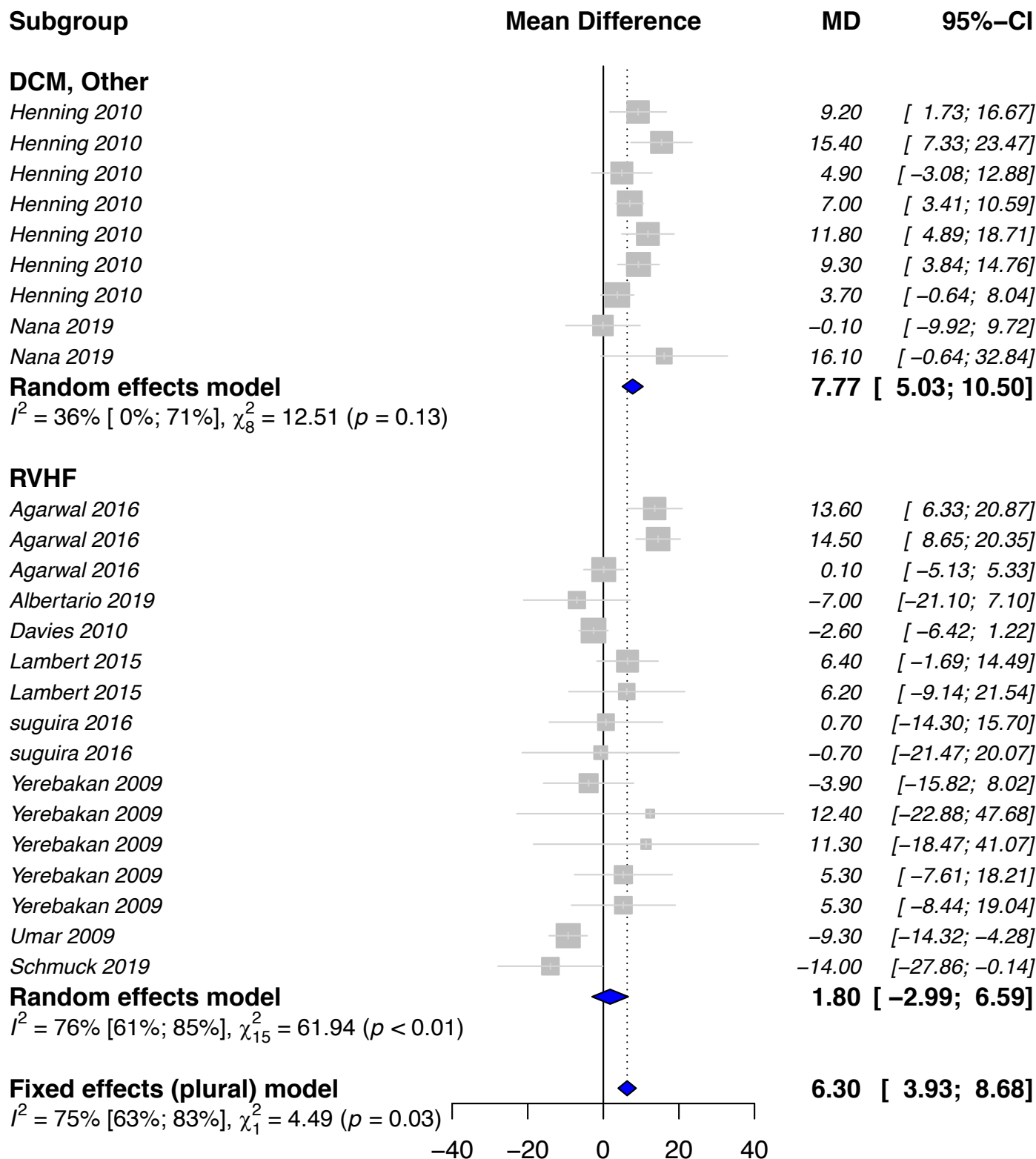
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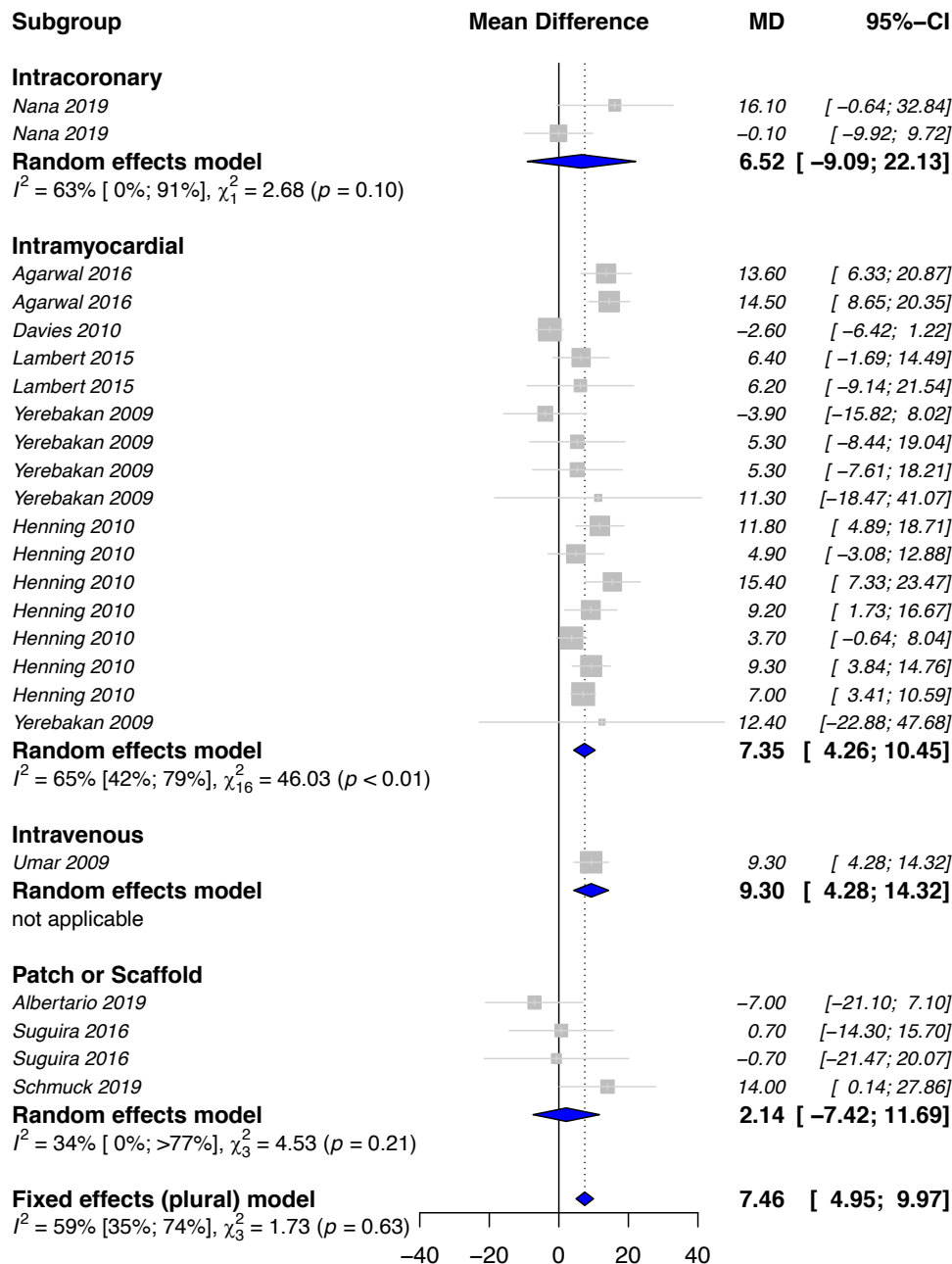


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276 **Supplemental 6. B) Cell-based effect on animal RVEF.**
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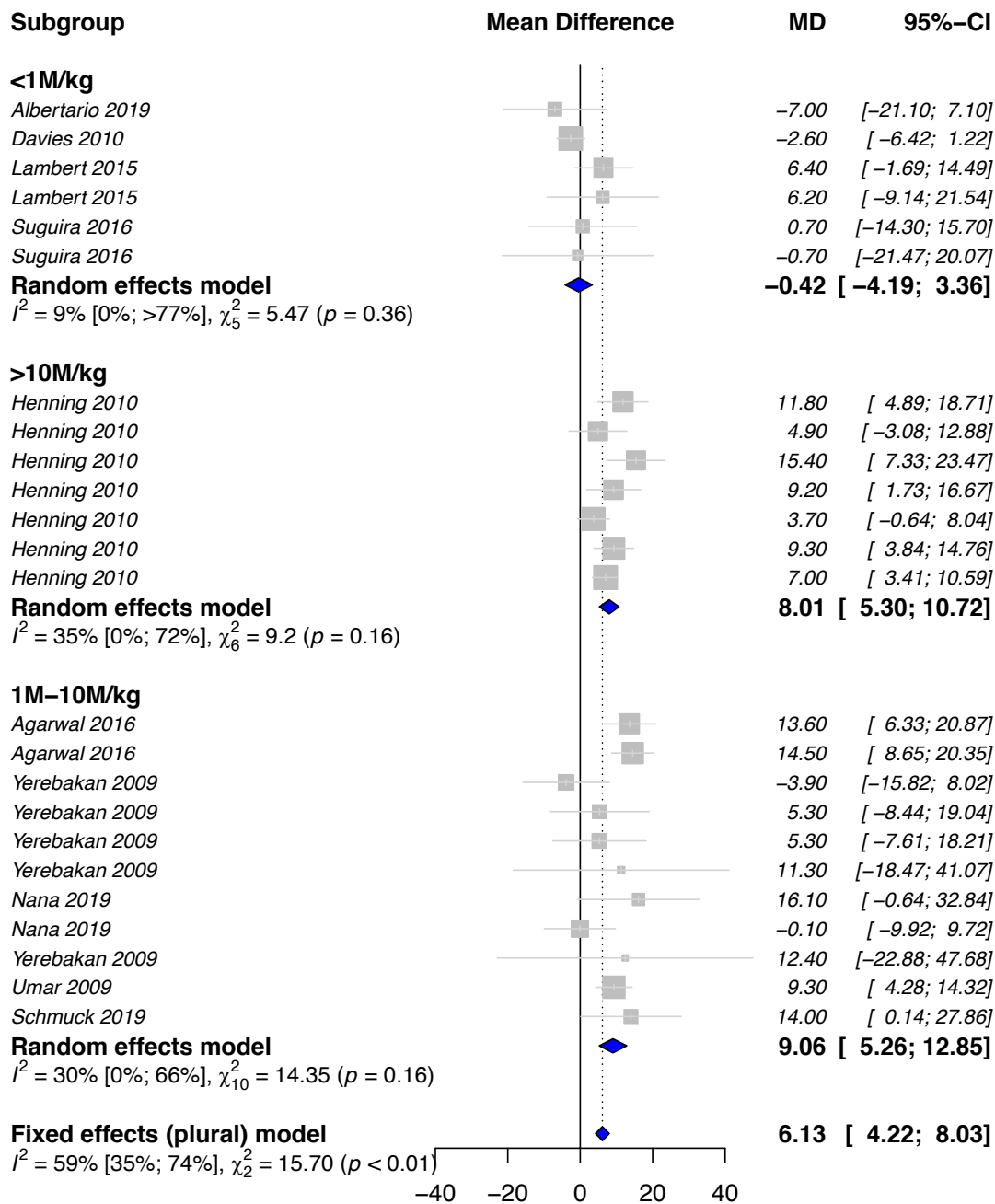


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282 **Supplemental 6. C) Cell-based effect on animal ejection fraction by disease**
283 **model.**

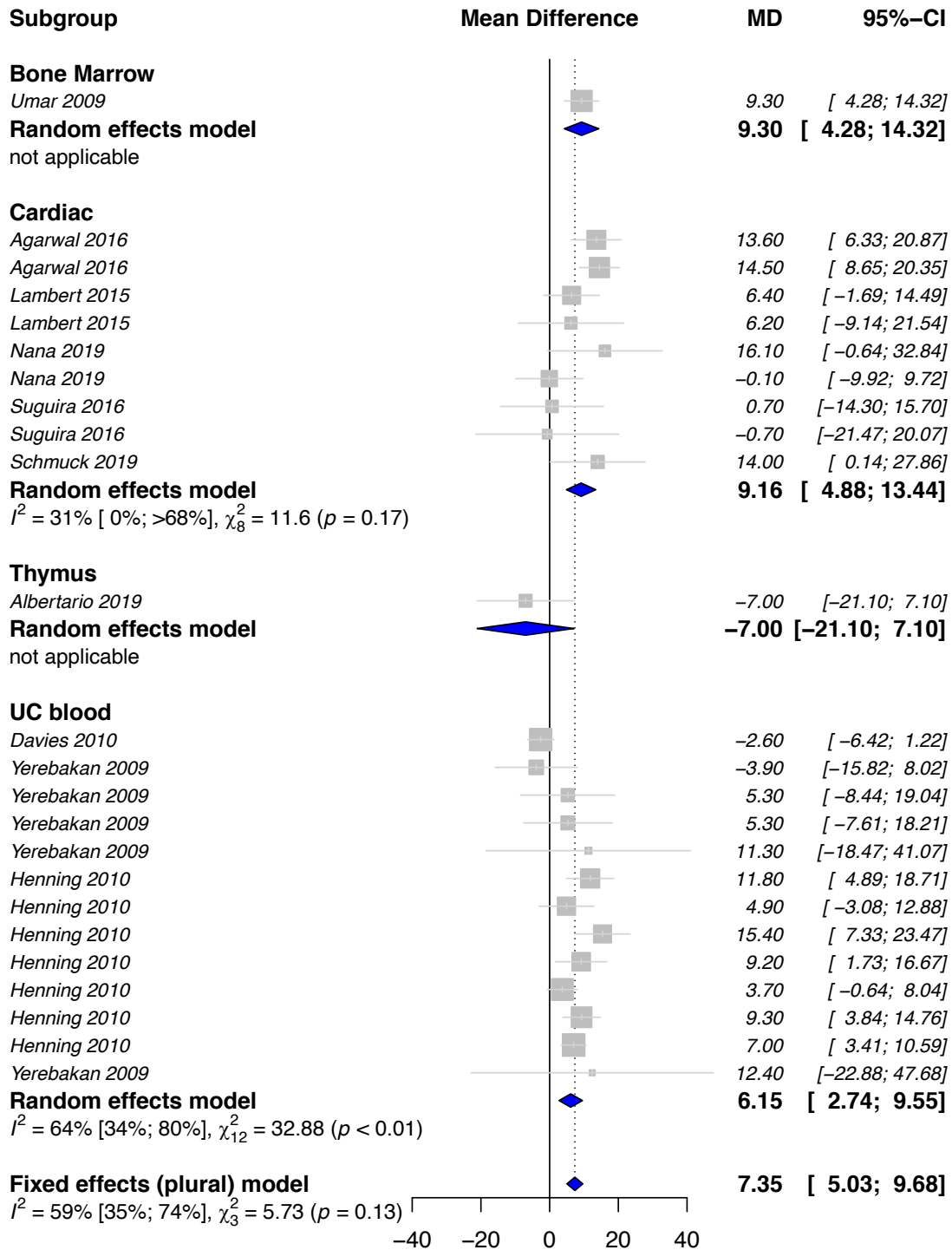
Supplemental 7. Subgroup analysis of regenerative cell effect size on animal ejection fraction. Forest plots demonstrating MD and 95% CI for A) Route of delivery, $p < 0.00001$ for intramyocardial injection. B) Dose, $p < 0.00001$ for 1-10 M. C) Tissue Source, $p < 0.0001$ for cardiac; $p = 0.0003$ for bone marrow. D) Timing of delivery, $p < 0.0001$ for 1 week–1 month. E) autologous vs. non-autologous sources, $p < 0.0001$ (non-autologous). Cell-based $n = 256$; Control $n = 261$.



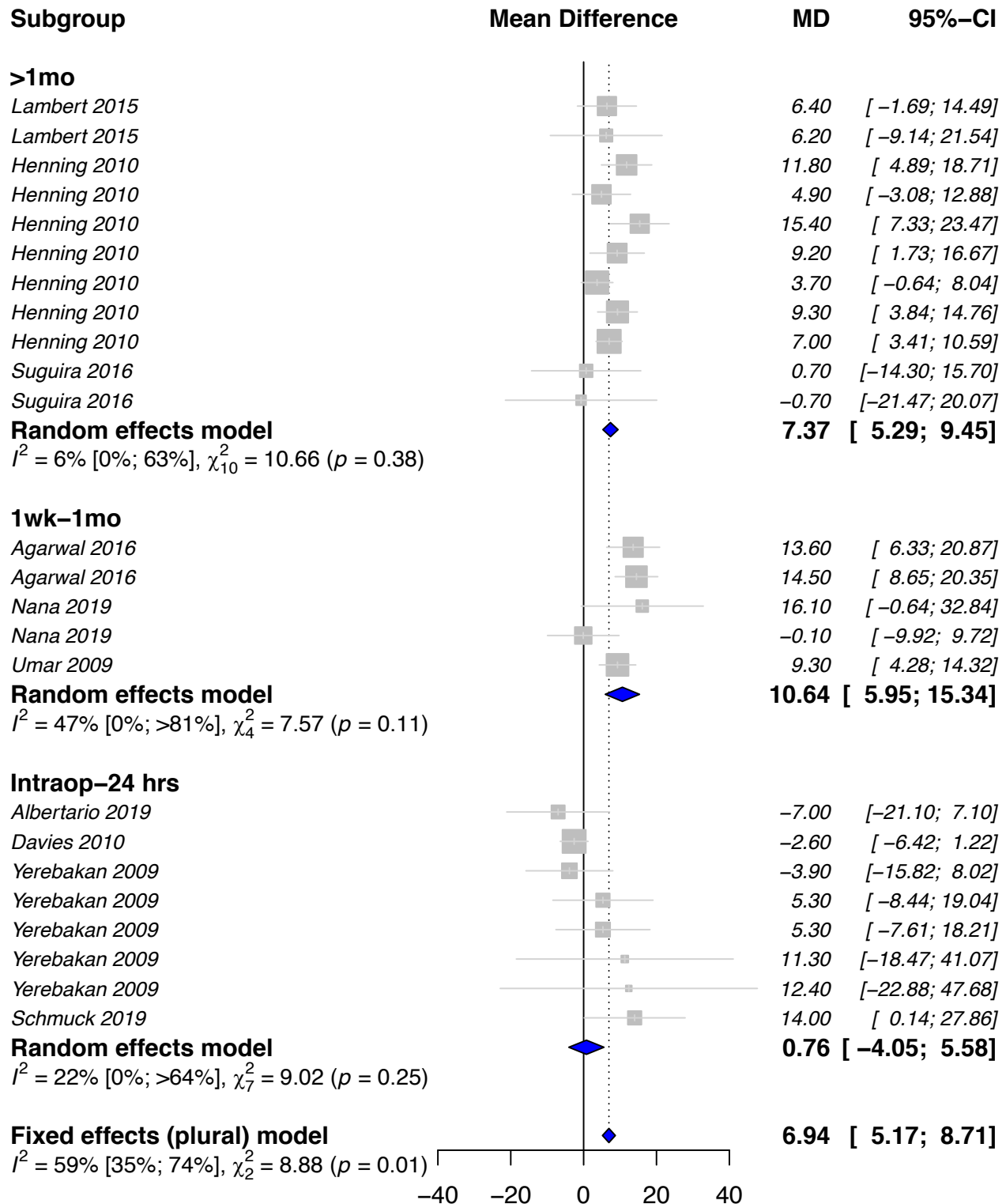
Supplemental 7. A) Cell-based effect on animal ejection fraction by route of delivery.



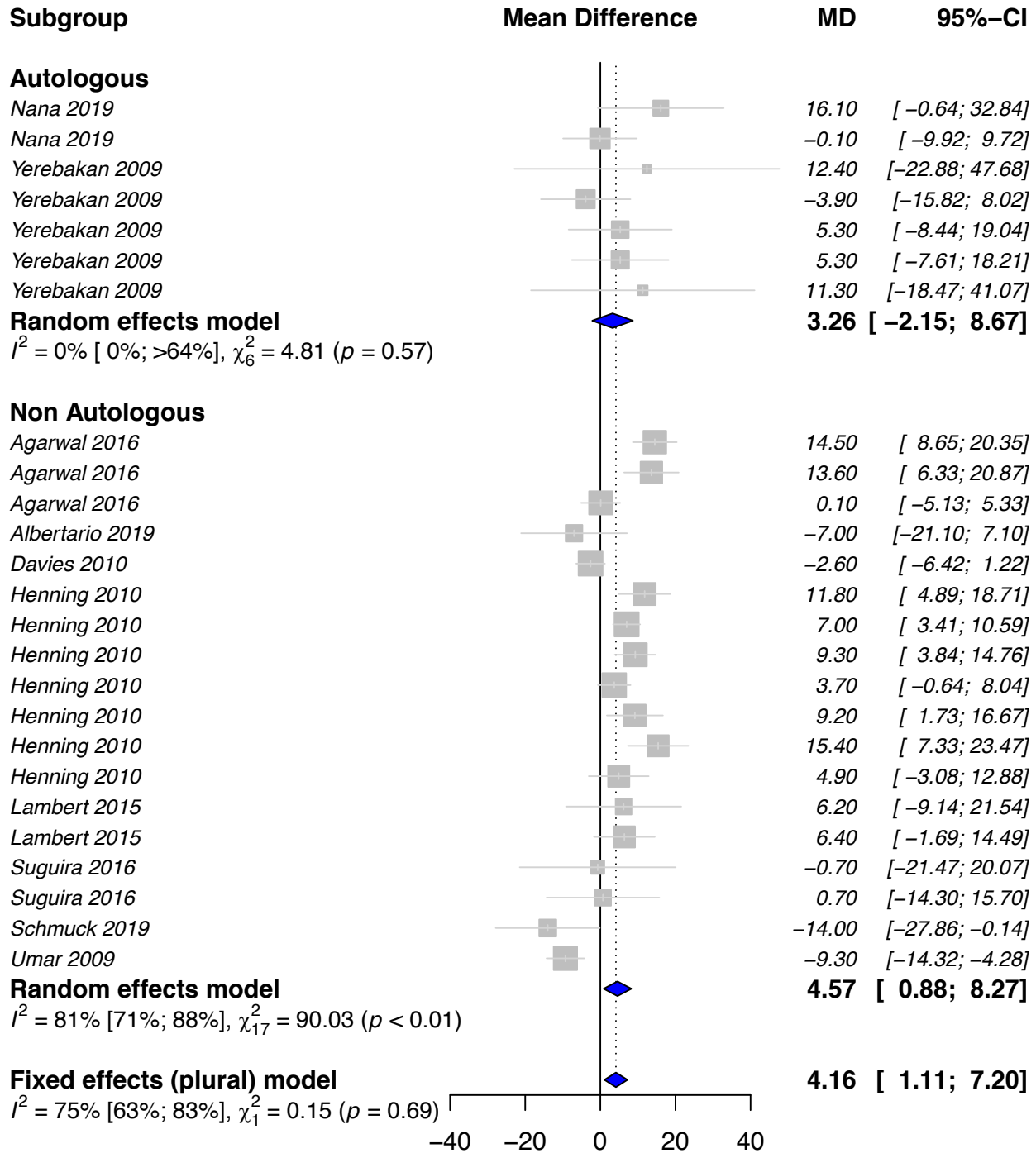
Supplemental 7. B) Cell-based effect on animal ejection fraction by dose.



Supplemental 7. C) Cell-based effect on animal ejection fraction by tissue source.

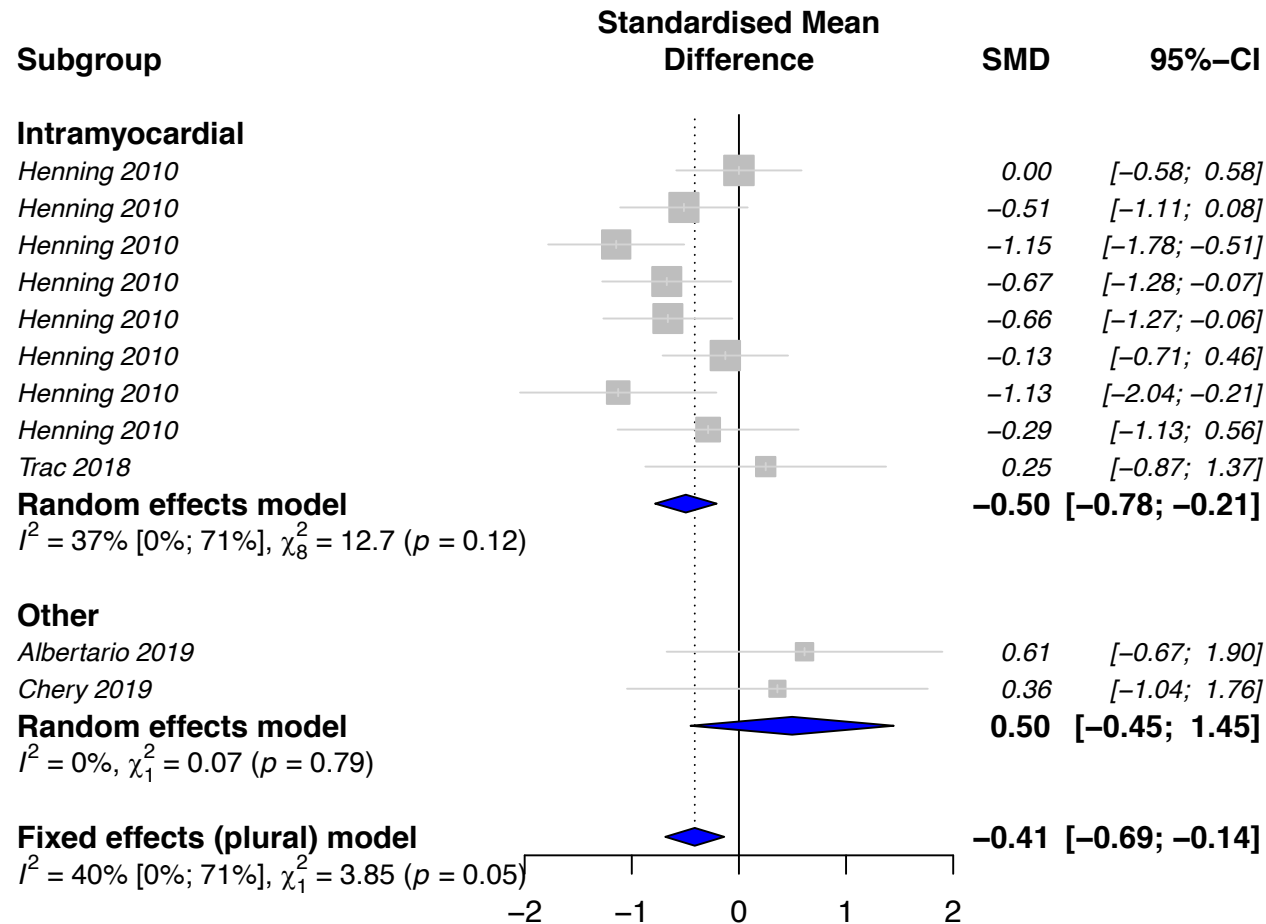


Supplemental 7. D) Cell-based effect on animal ejection fraction by timing of delivery.

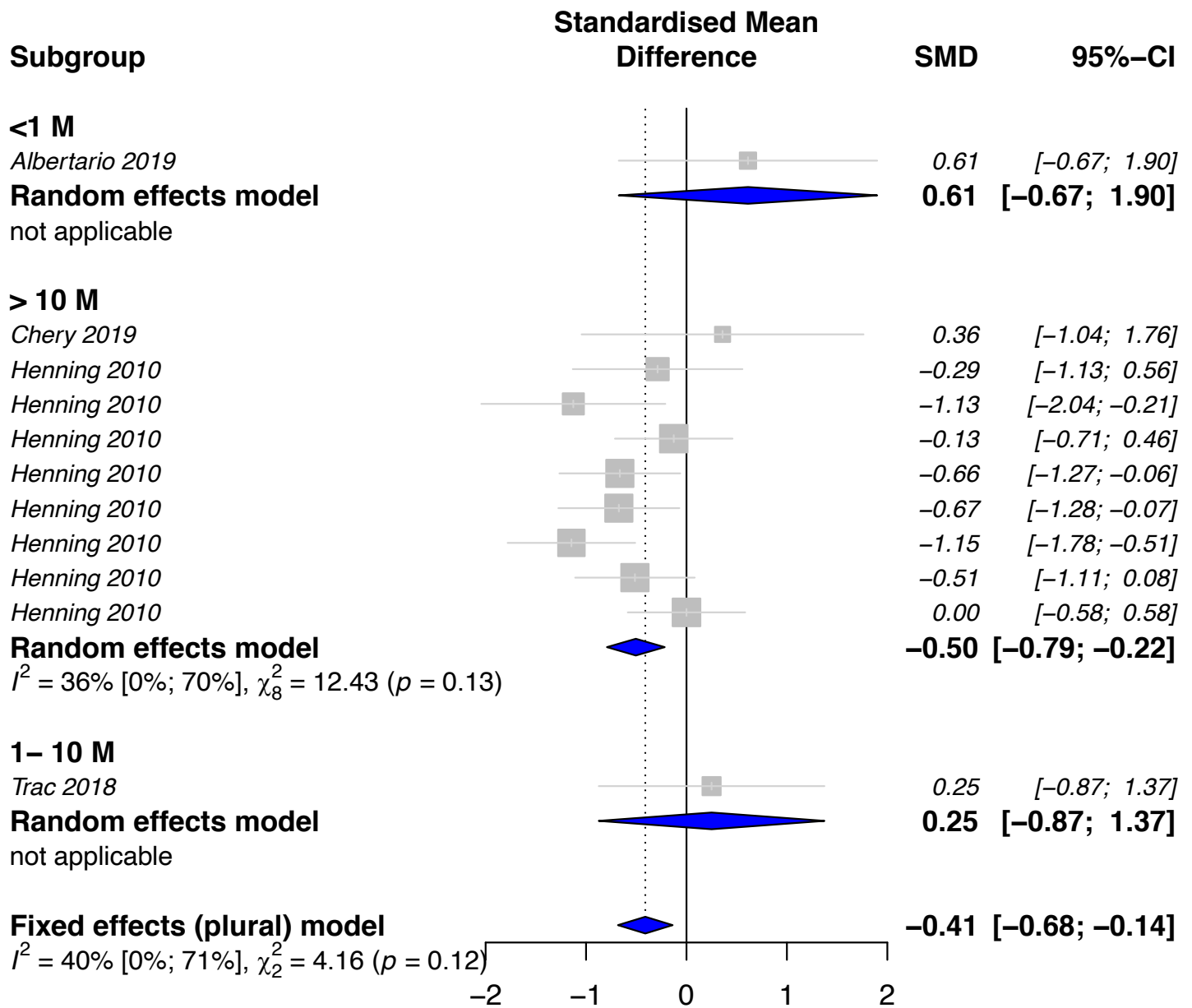


Supplemental 7. E) Cell-based effect on animal ejection fraction by autologous vs. non-autologous sources.

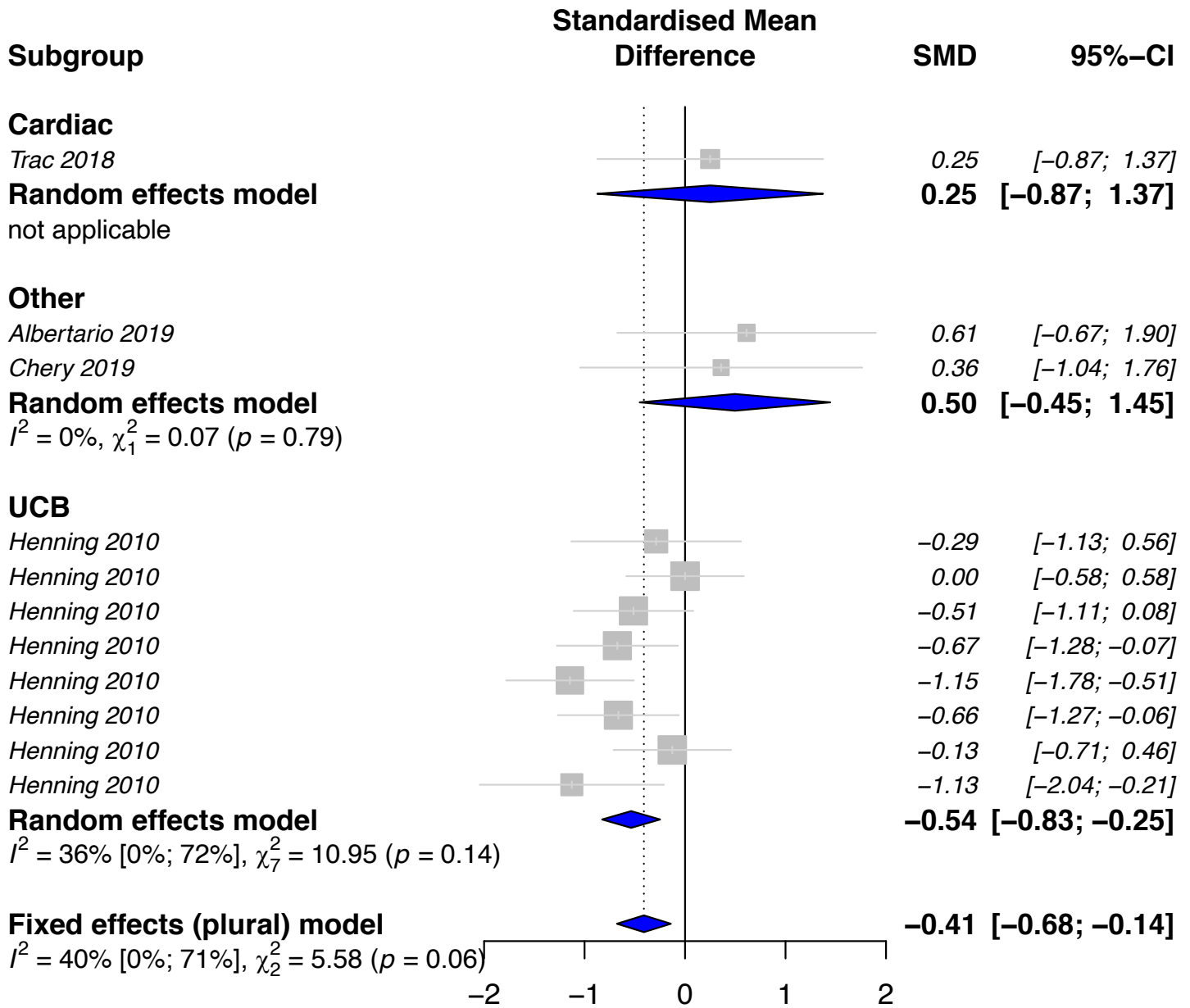
311 **Supplemental 8. Subgroup analysis of regenerative cell effect size on animal fractional shortening.** Forest
312 plots demonstrating MD and 95% CI for A) Route of delivery, $p=0.001$ for intramyocardial. B) Dose, $p=0.001$ for
313 >10 M cells/kg. C) Tissue Source, $p=0.001$ for umbilical cord blood. D) Timing of delivery, $p=0.001$ for >1
314 month. E) Disease model, $p=0.001$ for dilated cardiomyopathy. Cell-based $n=175$; Control $n=171$.
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316 **Supplemental 8. A) Cell-based effect on animal FS by route of delivery.**



Supplemental 8. B) Cell-based effect on animal FS by dose.

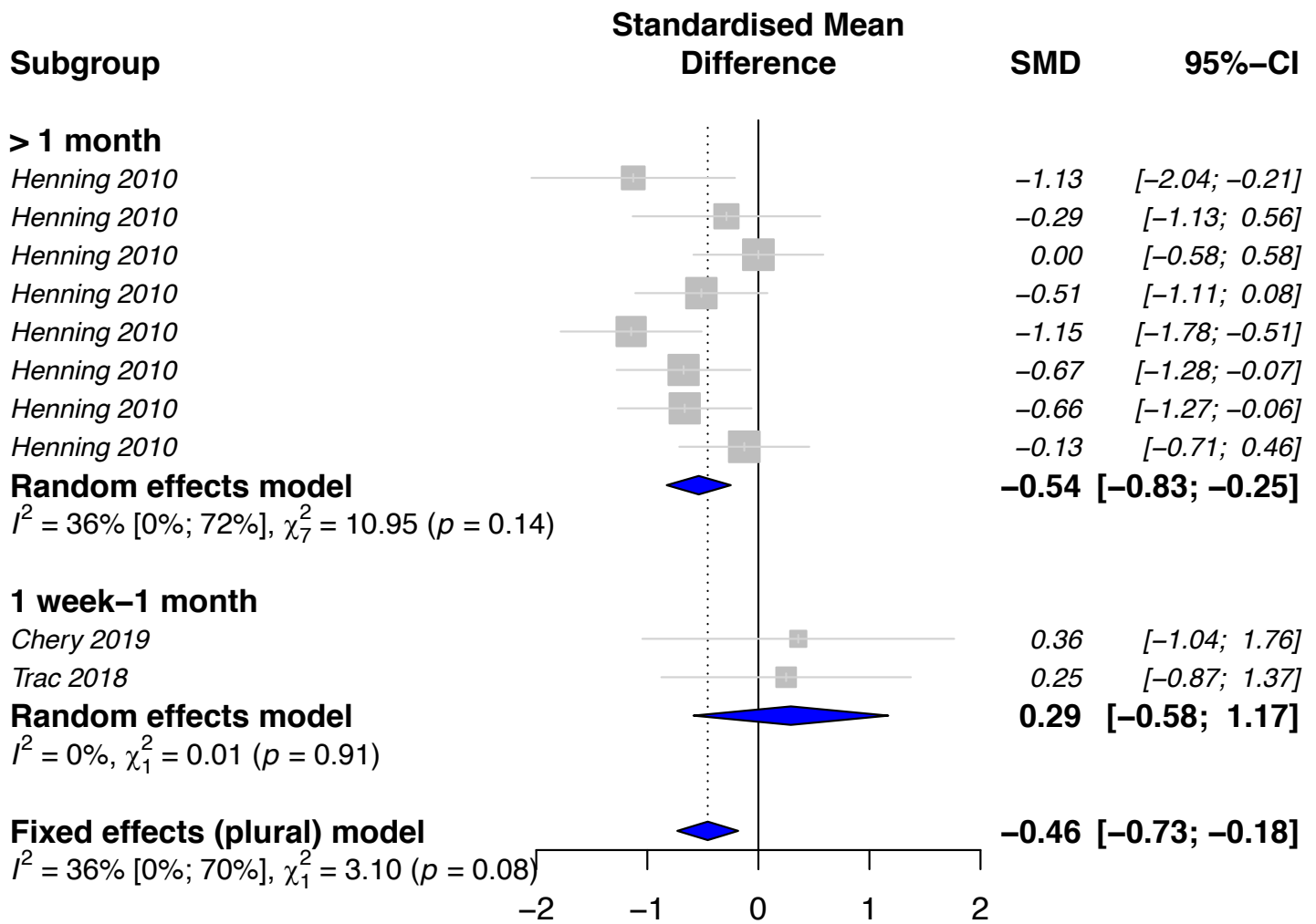


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329 **Supplemental 8. C) Cell-based effect on animal FS by tissue source.**

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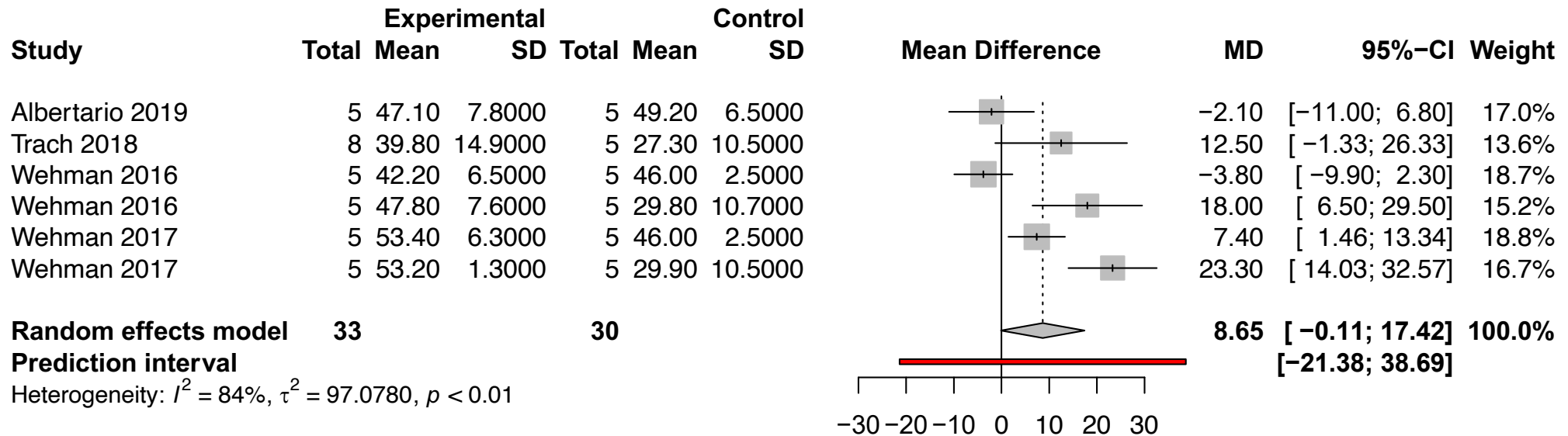
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Supplemental 8. D) Cell-based effect on animal FS by timing of delivery.

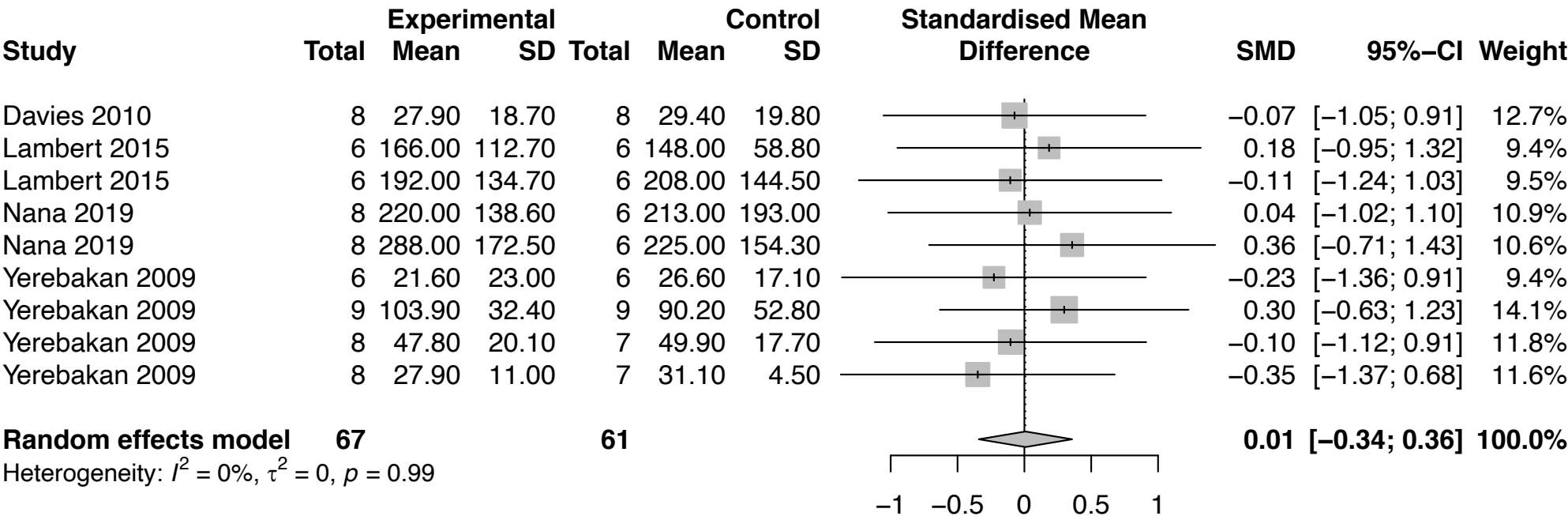
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355 **Supplemental 9. Effect size of regenerative cell on additional measures of animal cardiac function.** Forest
 356 plots demonstrating MD and 95% CI for A) Fractional area change, p=0.05; cell-based n= 33; control n=30. B)
 357 End diastolic volume, p=0.48; cell-based n=67; control n=61. C) End systolic volume, p=0.60; cell-based n=72;
 358 control n=66. D) Tricuspid annular plane systolic excursion, p=0.55; cell-based n=33; control n=58.



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 360 **Supplemental 9. A) Cell-based effect on animal FAC.**
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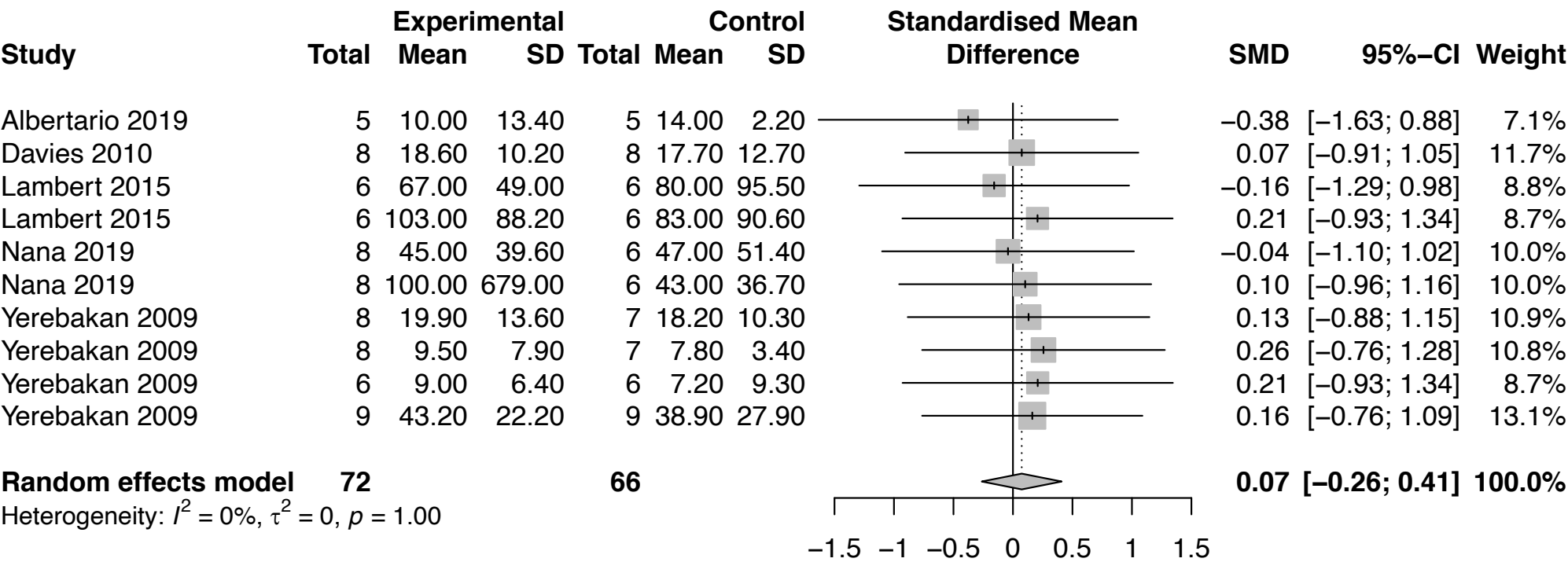
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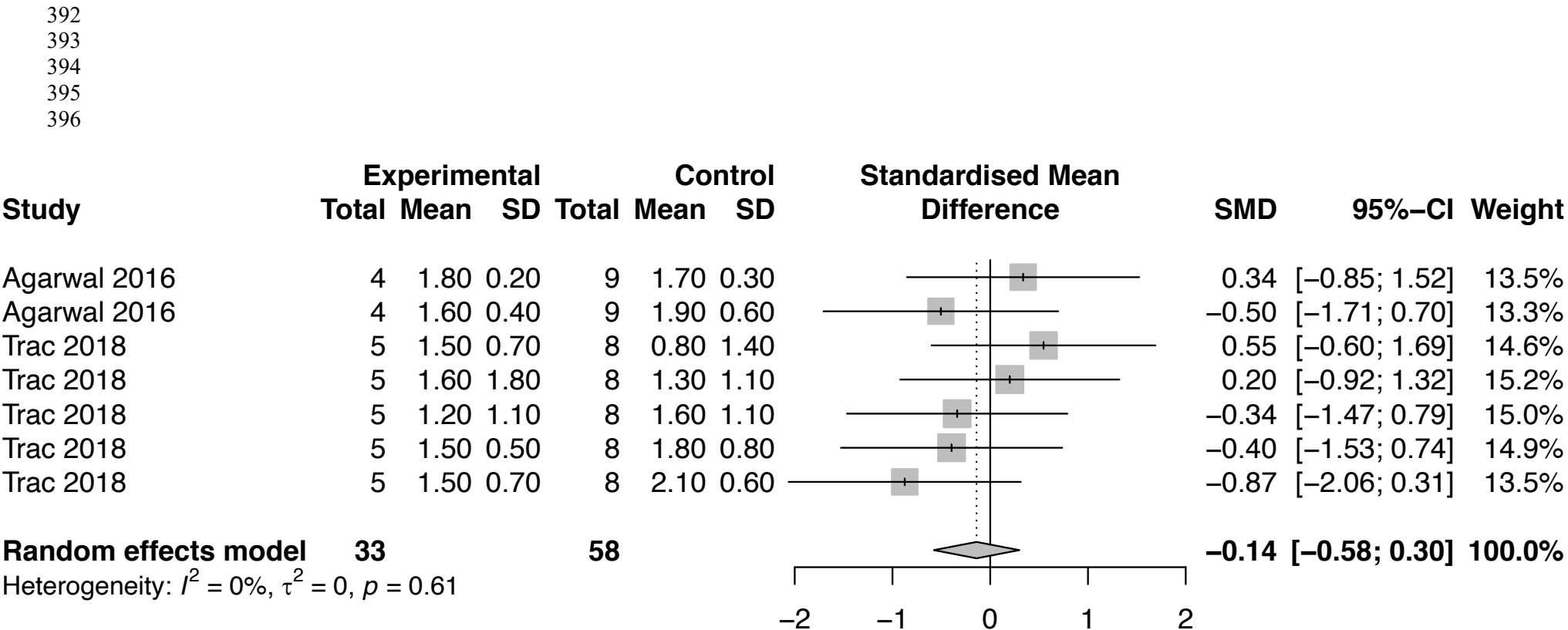
Supplemental 9. B) Cell-based effects on animal EDV.

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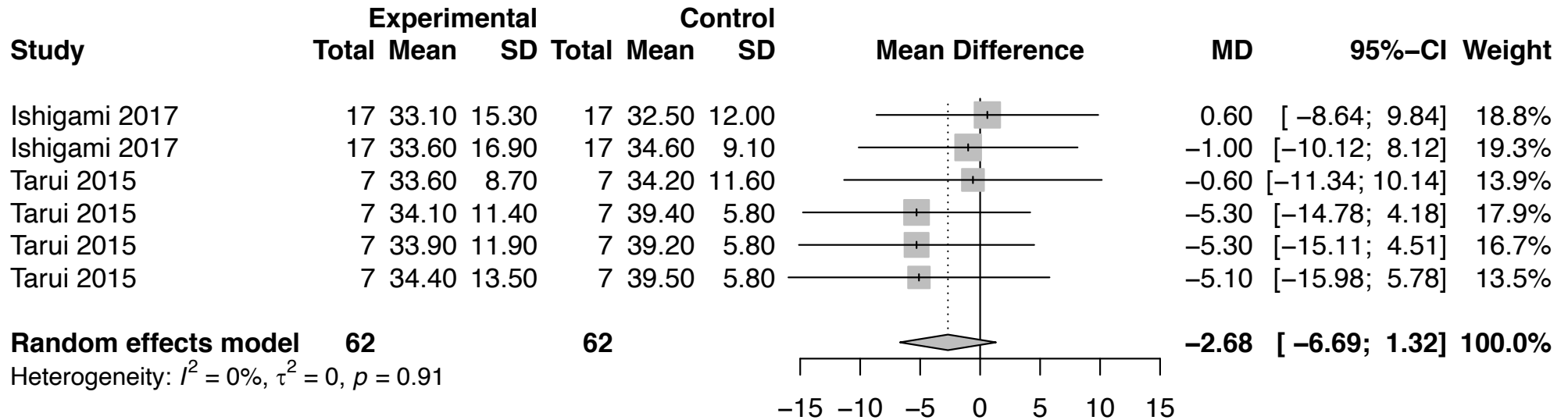
Supplemental 9. C) Cell-based effect on animal ESV.



Supplemental 9. D) Cell-based effect on Animal TAPSE.

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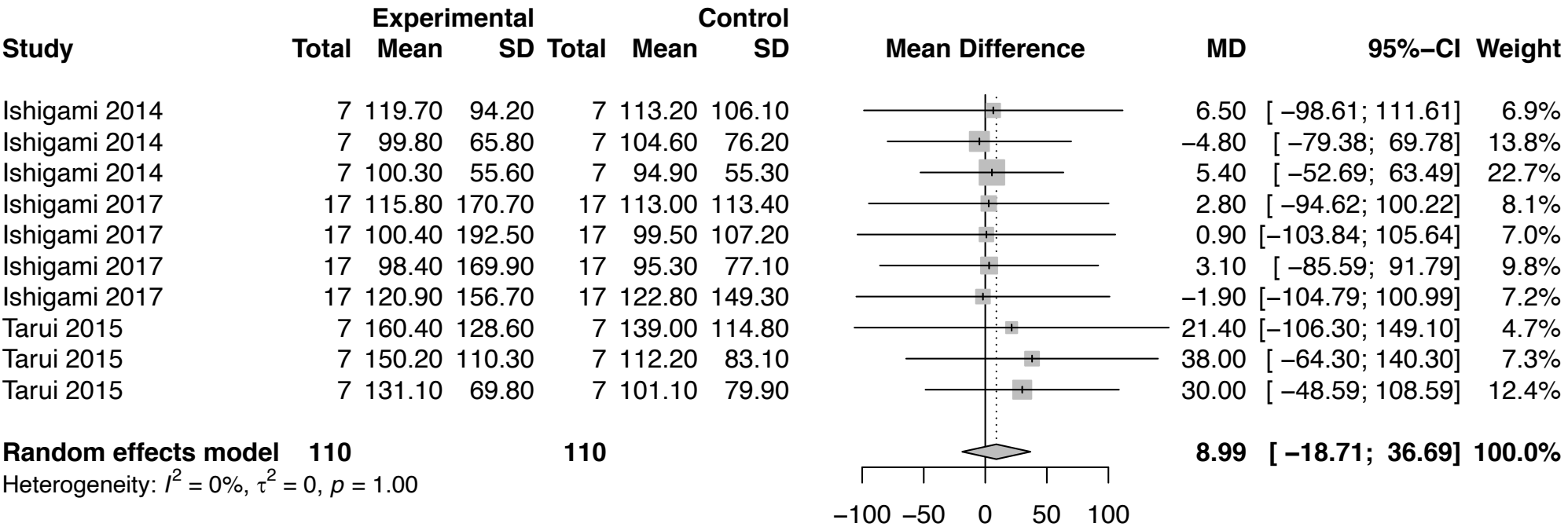
Supplemental 10. Effect size of regenerative cell on additional measures of human cardiac function. Forest plots demonstrating MD and 95% CI for A) Fractional area change, p=0.19; cell-based n=62; control n=62. B) End diastolic volume, p=0.52; cell-based n=110; control n=110. C) End systolic volume, p=0.96; cell-based n=110; control n=110.



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Supplemental 10. A) Cell-based effect on human FAC.

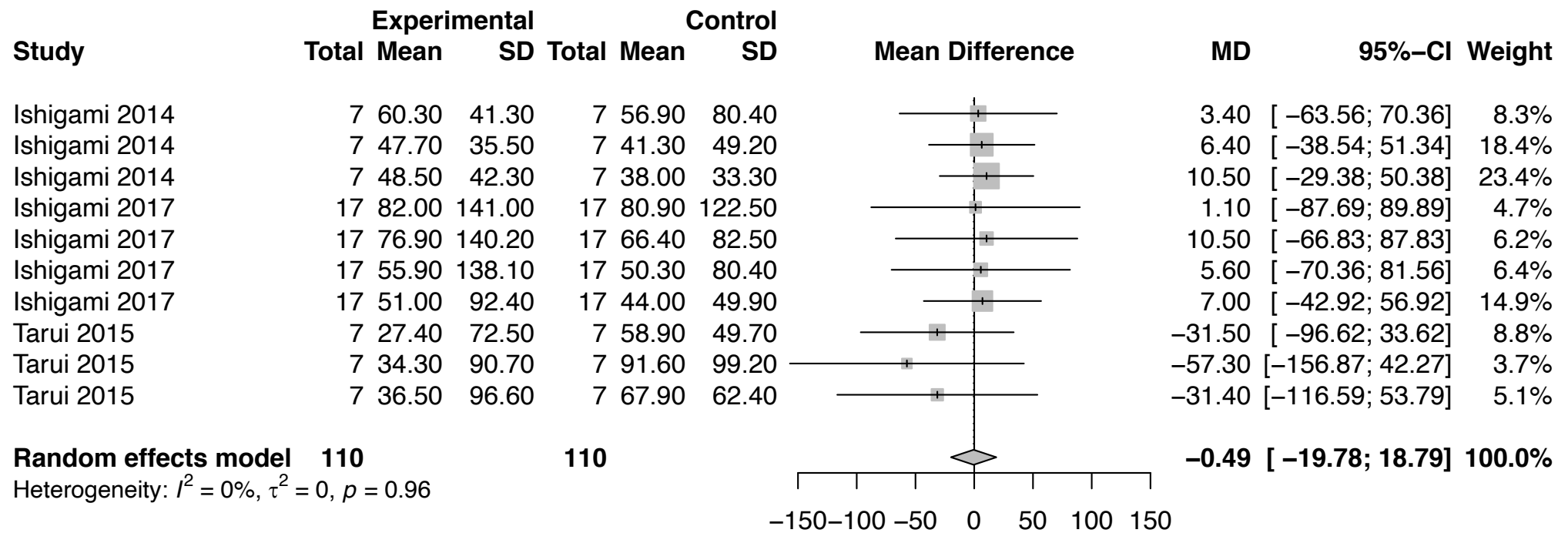
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Supplemental 10. B) Cell-based effect on human EDV.

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Supplemental 10. C) Cell-based effect on human ESV.

448 **Supplemental 11. SYRCLE risk of bias for animal studies.**

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| Author (Year) | Random sequence generation? | Groups similar at baseline? | Allocation concealed? | Animals randomly housed? | Blinding of caregivers and/or examiners? | Random selection for outcome assessment? | Blinding of outcome assessor? | Incomplete outcome data addressed? | Free from selective outcome reporting? | Free from other bias? |
|-----------------------|-----------------------------|-----------------------------|-----------------------|--------------------------|--|--|-------------------------------|------------------------------------|--|-----------------------|
| Agarwal (2016) | Yes | Yes | Yes | Unclear | Unclear | No | Yes | Yes | Yes | Yes |
| Albertario (2019) | Yes | Yes | No | Yes | Unclear | Unclear | Yes | Yes | Yes | Yes |
| Borenstein (2005) | Yes | Yes | Unclear | Unclear | Unclear | Unclear | Unclear | Yes | Yes | Yes |
| Brizard (2015) | Yes | Yes | Yes | Yes | Unclear | Unclear | Yes | Yes | Yes | Yes |
| Cao (2015) | Unclear | Yes | Unclear | Yes | Unclear | Unclear | Yes | Yes | Yes | Yes |
| Chery (2019) | Unclear | Yes | No | Unclear | Unclear | Unclear | Yes | Yes | Yes | Yes |
| Davies (2010) | Unclear | Yes | Unclear | Unclear | Unclear | Unclear | Unclear | Yes | Yes | No |
| Henning (2010) | Yes | Yes | Unclear | Unclear | Unclear | Unclear | Yes | Yes | Yes | Yes |
| Lambert (2015) | Unclear | Yes | Unclear | Unclear | Unclear | Unclear | Yes | Yes | Yes | Yes |
| Liu (2011) | Unclear | Yes | Unclear | Yes | Unclear | Unclear | Yes | Yes | Yes | Yes |
| Nana-Leventaki (2019) | Yes | Yes | Unclear | Yes | Unclear | Unclear | Yes | Yes | Yes | Yes |
| Schmuck (2019) | Yes | Yes | Unclear | Unclear | Unclear | Unclear | Yes | Yes | Yes | Yes |
| Sugiura (2016) | Yes | Yes | Unclear | Yes | Unclear | Unclear | Unclear | Yes | Yes | Yes |
| Trac (2018) | Yes | Yes | Unclear | Yes | Unclear | Unclear | Yes | Yes | Yes | Yes |
| Umar (2009) | Unclear | Yes | Unclear | Unclear | Unclear | Unclear | Yes | Yes | Yes | Yes |
| Wehman (2016) | Unclear | Yes | Unclear | Unclear | Unclear | Unclear | Yes | Yes | Yes | Yes |
| Wehman (2017) | Unclear | Yes | Unclear | Unclear | Unclear | Unclear | Yes | Yes | Yes | Yes |
| Yerebakan (2009) | Yes | Yes | Unclear | Unclear | Unclear | Unclear | Yes | Yes | Yes | Yes |

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Supplemental 12. ROBINS-I risk of bias for human studies.

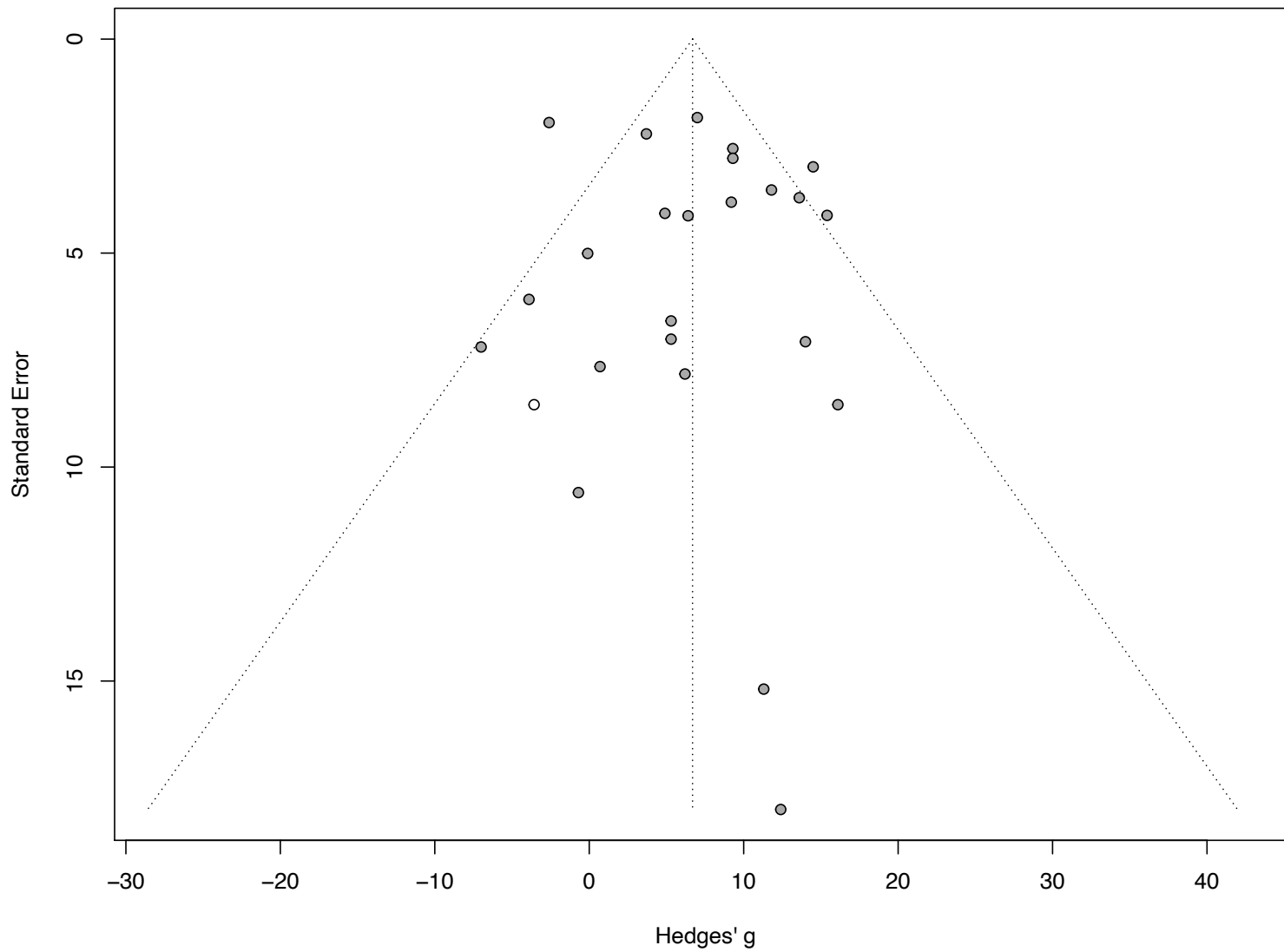
| | Risk of bias domains | | | | | |
|---------------|----------------------|----|----|----|----|---------|
| | D1 | D2 | D3 | D4 | D5 | Overall |
| Pincott 2017 | + | + | + | + | + | + |
| Rupp 2010 | X | + | + | - | - | X |
| Burkhart 2019 | X | + | + | - | + | X |
| Qureshi 2017 | X | + | + | - | + | X |
| Sano 2018 | X | + | + | + | + | X |
| Ishigami 2017 | + | + | + | - | + | - |
| Ishigami 2014 | - | + | + | - | + | - |
| Rupp 2012 | X | + | + | - | + | X |
| Zchirnt | X | + | + | - | + | X |
| Burkhart 2015 | X | + | + | - | + | X |
| Rivas 2011 | X | + | + | - | + | X |
| Eitoku 2018 | X | + | + | - | + | X |
| Tarui 2015 | X | + | + | - | + | X |

Domains:
D1: Bias due to randomisation.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing data.
D4: Bias due to outcome measurement.
D5: Bias due to selection of reported result.

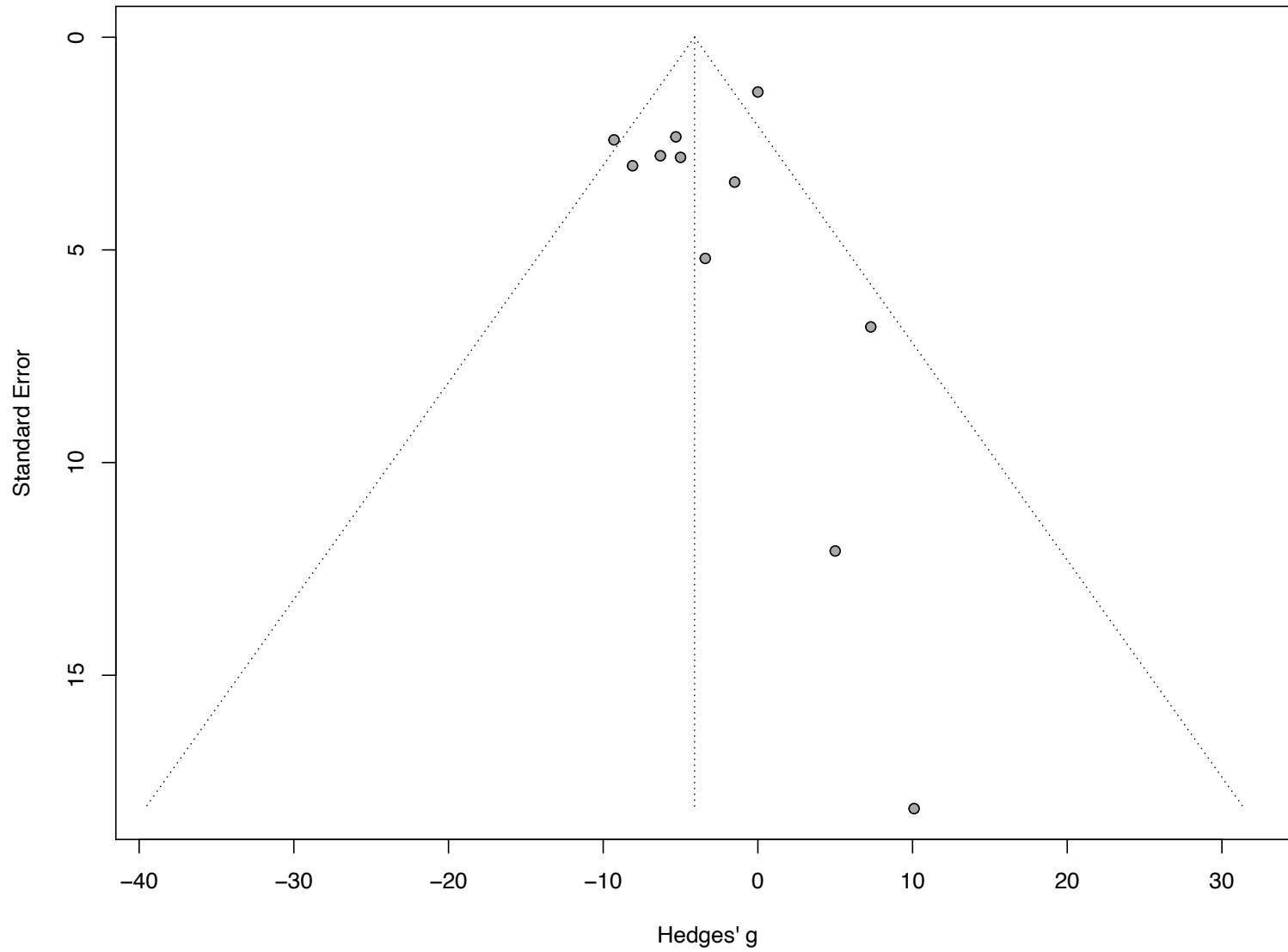
Judgement
X High
- Some concerns
+ Low

460 **Supplemental 13. Funnel plot diagram for animal ejection fraction.**

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462 **Supplemental 14. Funnel plot diagram for animal fractional shortening.**



463 **Supplemental Table 1. Animal study intervention characteristics.**

| Animal Characteristics | n (%) |
|-------------------------------|--------------|
| <i>Disease model</i> | |
| RVHF | 307 (80%) |
| DCM | 45 (12%) |
| Autoimmune myocarditis | 22 (6%) |
| Infant cardiopulmonary bypass | 12 (3%) |
| <i>Species</i> | |
| Rats | 120 (31%) |
| Sheep | 118 (31%) |
| Rabbit | 50 (13%) |
| Hamsters | 45 (12%) |
| Swine | 42 (11%) |
| Ram | 11 (3%) |
| <i>Age</i> | |
| ≤ 1 month | 143 (37%) |
| >1 month | 128 (33%) |
| Did Not Report | 115 (30%) |

| Intervention Characteristics | n (%) |
|-------------------------------------|--------------|
| <i>Cell route</i> | |
| Intravenous | 140 (36%) |
| Intramyocardial | 135 (35%) |
| Graft/Patch/Sheet | 61 (16%) |
| Intracoronary | 34 (9%) |
| Epicardial | 16 (4%) |
| <i>Cell dose</i> | |
| < 1M/kg | 109 (28%) |
| ≥ 1M and < 10M/kg | 157 (41%) |
| ≥ 10M/kg | 120 (31%) |
| <i>Cell source</i> | |
| Cardiac | 107 (28%) |
| Umbilical cord blood | 93 (24%) |
| Bone marrow | 80 (21%) |
| Adipose | 70 (18%) |
| Thymus | 25 (6%) |
| Skeletal muscle | 11 (3%) |
| <i>Timing</i> | |
| Intraoperative and < 24 hours | 79 (20%) |
| ≥ 24 hours and < 1 week | 0 (0%) |
| ≥ 1 week and < 1 month | 100 (26%) |
| ≥ 1 month | 177 (46%) |
| Did Not Report | 30 (8%) |

465 **Supplemental Table 2. Adverse events by systems.**

| Acute Adverse Events | |
|---------------------------------------|---|
| Systemic | |
| Allergic reaction / Anaphylaxis | Delayed Adverse Events |
| Death | |
| Elevated CRP | Systemic |
| Fever | Late death |
| Hemodynamic instability / Hypotension | Cardiac |
| Malignancy | Late heart failure |
| Tumor formation | Unplanned Interventions |
| Respiratory | |
| Bronchitis | BCPS or TCPC take down |
| Chest tube | Catheterizations |
| Death - Respiratory | Heart transplant |
| Pleural effusion | Intubation |
| Pneumonia | Pacemaker implantation |
| Cardiac | Unplanned Hospitalizations |
| APCA coil occlusion | |
| Arrhythmia | CCU admission |
| Bradycardia | ED visit |
| Cardiac tamponade | General wards/floor admission |
| Cardiac-related pneumothorax | Rehospitalization for heart failure |
| Cardiopulmonary resuscitation | APCA = aortopulmonary collateral artery BCPS = bidirectional cavopulmonary shunt CCU = cardiac/coronary care unit ED = emergency department TCPC = total cavopulmonary connection |
| Coronary spasm | |
| Death - Cardiac | |
| ECMO | |
| Epicardial bleed | |
| Heart failure | |
| Myocardial ischemia | |
| Palpitations | |
| Valve malfunction | |
| Neurological | |
| Seizure | |
| Stroke | |
| Hematological | |
| Embolism | |
| Thromboembolic events | |
| GI | |
| Cirrhosis | |
| Protein-losing enteropathy | |
| Renal | |
| Renal deterioration | |
| Infectious disease | |
| Infection | |

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468 **Supplemental Table 3. Animal adverse events.**

| Adverse Event | Control | | Cell-based | | Overall |
|--------------------|---------|-------|------------|-------|--------------------|
| | Events | Total | Events | Total | Peto OR (95% CI) |
| Cardiac | 13 | 73 | 8 | 74 | 0.48 (0.17, 1.33) |
| Respiratory | 5 | 69 | 8 | 67 | 2.29 (0.67, 7.84) |
| GI | 0 | 69 | 0 | 67 | - |
| Hematologic | 0 | 69 | 0 | 67 | - |
| Infectious disease | 0 | 69 | 0 | 67 | - |
| Systemic | 1 | 69 | 0 | 67 | 0.44 (0.02, 12.01) |
| Overall | 19 | 418 | 16 | 409 | 0.89 (0.43, 1.83) |

469 Supplemental Table 4. Human study intervention characteristics.

| Human Characteristics | n (%) |
|---------------------------|-----------|
| <i>Disease</i> | |
| SV | 142 (66%) |
| HLHS | 41 (19%) |
| DCM | 32 (15%) |
| <i>Cell route</i> | |
| Intracoronary | 204 (95%) |
| Intramyocardial | 11 (5%) |
| <i>Cell dose</i> | |
| < 1M/kg | 170 (79%) |
| ≥ 1M and < 10M/kg | 35 (16%) |
| ≥ 10M/kg | 0 (0%) |
| Did Not Report | 10 (5%) |
| <i>Cell source</i> | |
| Cardiac | 170 (79%) |
| Bone marrow | 34 (16%) |
| Umbilical cord blood | 11 (5%) |

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471 **Supplemental Table 5. Human adverse events.**

| Adverse Event | Control | | Cell-based | | Overall |
|--------------------|---------|-------|------------|-------|--------------------|
| | Events | Total | Events | Total | Peto OR (95% CI) |
| Cardiac | 81 | 101 | 41 | 82 | 0.11 (0.05, 0.23) |
| Respiratory | 5 | 101 | 0 | 82 | 0.16 (0.03, 0.95) |
| GI | 2 | 101 | 0 | 82 | 0.14 (0.01, 2.16) |
| Hematologic | 7 | 101 | 2 | 82 | 0.44 (0.11, 1.75) |
| Infectious disease | 1 | 101 | 0 | 82 | 0.19 (0.00, 10.05) |
| Systemic | 2 | 101 | 1 | 82 | 0.74 (0.07, 7.54) |
| Overall | 98 | 606 | 44 | 492 | 0.17 (0.09, 0.30) |

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483 **Supplemental Table 6. Clinical trials, ongoing.**

| Sponsor | Disease | Methods | Participants | Interventions | Comparison | Outcome | Notes |
|-------------|--------------------------------|---|--|---|--------------------------------|---------------------|------------|
| NCT03779711 | HLHS | Phase II treatment given at time of stage II surgical repair | Children <9 months of age with HLHS or HLHS variant with single ventricular dependent CHD having undergone Stage I surgical repair and Stage II surgical repair | Biologic: Autologous UCB derived mononuclear cells Procedure: Stage II surgical repair | Stage II surgical repair alone | Efficacy | Recruiting |
| NCT03525418 | HLHS | Phase I/II: First treatment given at time of stage II surgical repair Second treatment given at time of stage II surgical repair vs. placebo | HLHS (all types) requiring stage II surgical intervention | Biologic: Bone marrow derived MSCs Procedure: Stage II surgical repair | Stage II surgical repair alone | Safety and Efficacy | Recruiting |
| NCT03431480 | HLHS | Phase I open label safety study | Male and females with antenatally diagnosed HLHS (all types requiring Norwood operation) | Biologic: Autologous human placental cord blood mononuclear cells Procedure: Stage I surgical repair | N/A | Safety and Efficacy | Recruiting |
| NCT03079401 | HLHS AV Canal Defects | Phase I/II | Patient with a history of single ventricle palliation undergoing bidirectional Glenn with LV recruitment procedures or those patients undergoing LV recruitment procedures | Biologic: Mesenchymal progenitor cells | Surgical repair alone | Safety and Efficacy | Recruiting |
| NCT02781922 | HLHS SV | Phase III single blind parallel group study | Functional single ventricle patient with HF scheduled for stage 2 (Glenn) or stage 3 (Fontan) surgery | Biologic: Autologous cardiac stem cells | Surgical repair alone | Safety and Efficacy | Unknown |

| | | | | | | | |
|-------------|------|---------|---|---|-----|--------|------------|
| | | | EF < 55% | | | | |
| NCT01883076 | HLHS | Phase I | Individuals with HLHS who have undergone Stage I surgical palliation and undergoing planned Stage II Palliative Glenn Surgery | Biologic: autologous umbilical cord blood cells | N/A | Safety | Recruiting |

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